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PUNCTURES OF THE BRAIN

THE FACTORS CONCERNED IN GLIOSIS AND IN CICATRICIAL CONTRACTION *

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AND
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NEW YORK

In a series of experimental punctures of the brain performed by one of us,[1] it was observed that, in addition to the usual scar composed of connective tissue and neuroglia, open tracks which did not contain any connective tissue and which were surrounded by little if any gliosis occasionally resulted. In the hope of explaining these variations, we have compared the result obtained from leaving injured brain tissue in place with the result following removal of an equal portion of such tissue. The investigation has thrown light on certain factors controlling gliosis and points to a fundamental principle involved in surgery of the brain.

LITERATURE

In general, the literature shows that wounds produced in experimental puncture of the brain have frequently been made by heated blunt needles (Tschistowitsch,[2] Coen,[3] Macklin and Macklin [4] and others). This produces a wide zone of injured tissue. The conclusions reached by these investigators was that the primary rôle in repair was played by elements in the connective tissue, the reaction of neuroglia being a secondary process. In all the work attention has been called to the formation of a connective tissue core which replaces the injured tissue of the brain, and to the reaction in the surrounding cerebral tissue.

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* Read at the Fifty-Third Annual Meeting of the American Neurological Association, Atlantic City, N. J., May 24, 1927.

* From the Laboratory of Neurocytology, Presbyterian Hospital, Department of Surgery, Columbia University.

1. Penfield, W.: Meningocerebral Adhesions, Surg. Gynec. Obst. **39**:803, 1924.
2. Tschistowitsch: Ueber die Heilung aseptischer traumatischer Gehirnverletzungen, Beitr. z. Path. Anat. u. z. allg. Pathol. **23**:321, 1898.
3. Coen, E.: Ueber die Heilung von Stickwunden des Gehirnes, Beitr. z. Physiol. **2**:107, 1887.
4. Macklin, M. F., and Macklin, C. C.: Study of Brain Repair in the Rat by Use of Trypan Blue with Special Reference to Vital Staining of Macrophages, Arch. Neurol. & Psychiat. **3**:353 (April) 1920.

Del Rio-Hortega and Penfield [5] described in detail the changes occurring in neuroglia astrocytes about stab wounds, showing that multiplication begins as early as the fourth day and is followed by the formation of fibers and by a radiating arrangement of the cells. At the center of such tracks a strong connective tissue core was always found.[1] It is of interest to note that Wilson,[6] while studying tracks made in the human brain with a blunt needle, observed that the connective tissue core replaced the injured brain except in the deeper parts, in which a hollow space was frequently noted. He also observed that the reaction was more prominent in the gray matter and less marked in the white matter, but he concluded that the neuroglial elements played only a small part in the repair.

Puncture of the brain as first suggested for clinical use by Neisser [7] and Pollak involved the removal of a cylinder of cerebral tissue in an open hollow needle. In exploratory puncture, as generally employed by neurologic surgeons, a blunt needle provided with a lateral opening for the entrance of fluid is used. The result of puncture of the brain has been studied histologically by various authors on both human and experimental material.

The following experiments using these two methods may be divided accordingly into two series. In one series, punctures were made by a sterile blunt brain needle, and in the other, punctures were made by a sterile open cannula of the same caliber. In the latter instance, the injured tissue of the brain was reamed out by the cannula and removed.

TECHNIC

Experiments were carried out as follows: Bilateral craniotomies were performed on dogs, openings being made in the skull 2 by 3 or 4 cm. in extent. The dura was then incised and reflected. A small incision was made in the pia-arachnoid, and a blunt exploratory brain needle, such as is commonly employed in neurologic operations, was passed into the brain to a depth of about 1.5 cm. This was repeated once or twice. On the opposite side of the head a similar craniotomy was performed, but here an open cannula of the same diameter and with a rounded edge was used to ream out and remove a core of brain tissue from the opposite hemisphere. The dura was then replaced on both sides and sutured with silk when possible and the muscle closed in separate layers. Six cerebral punctures were made in each of seven dogs. Neither type of needle caused noticeable hemorrhage. Recovery was uneventful. At intervals up to seventy-nine days, the animals were killed by etherization and perfusion of a carotid artery with 10 per cent liquor formaldehydi. The brain tissue and over-

5. Del Rio-Hortega, P., and Penfield, W.: Cerebral Cicatrix. The Reaction of Neuroglia and Microglia to Brain Wounds, Bull. Johns Hopkins Hosp. **41**: 278, 1927.

6. Wilson, R. B.: Brain Repair, Arch. Neurol. & Psychiat. **15**:75 (Jan.) 1926.

7. Neisser, E.: Die Hirnpunktion, Med. Klin. **22**:43, 1926.

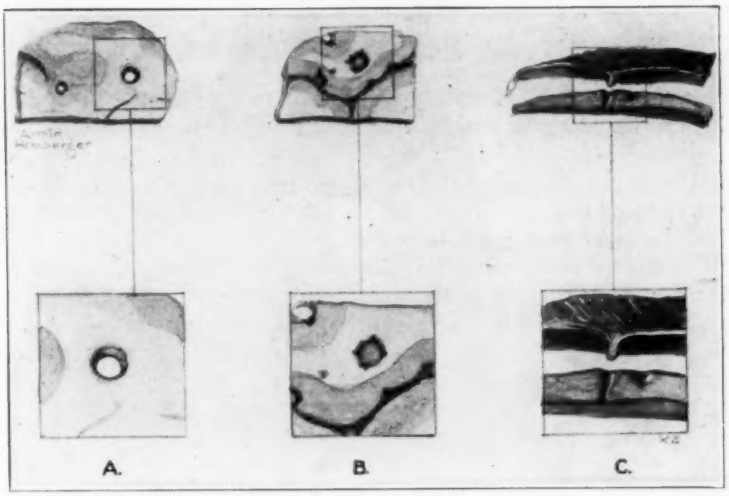

Fig. 1.—*a* indicates a sharply marked off empty track left by the hollow needle; twenty-six days; *b*, irregular core filling track made by blunt-nosed brain needle; twenty-six days, and *c*, connective tissue core, adherent to overlying meninges and muscle, pulled out from the underlying brain; twenty-six days after making stab wound with blunt nosed needle.

Fig. 2.—Brain with dura and muscle overlying track of blunt needle. The connective tissue core is darker than the brain.

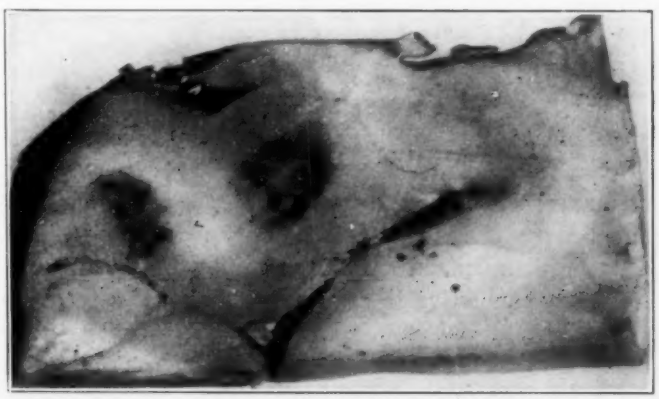

Fig. 3.—Closed tracks left by punctures made with the blunt needle. Note the surrounding blood vessels.

lying muscle were then cut out and removed in a single block without disturbing existing relationships. Experiments designed to study blood supply are described later.

The staining technic was as follows: Blocks were fixed in Cajal's formaldehyde-ammonium-bromide solution, in 10 per cent liquor formaldehydi, and in Zenker's solution. Sections were made at right angles to the tracks in most cases and stained by the following methods: Cajal's gold chloride sublimate, hematoxylin-eosin, silver carbonate for connective tissue, silver carbonate for astrocytes, Mallory's eosin methylene blue, and by von Gieson's and Mallory's phosphotungstic acid methods.

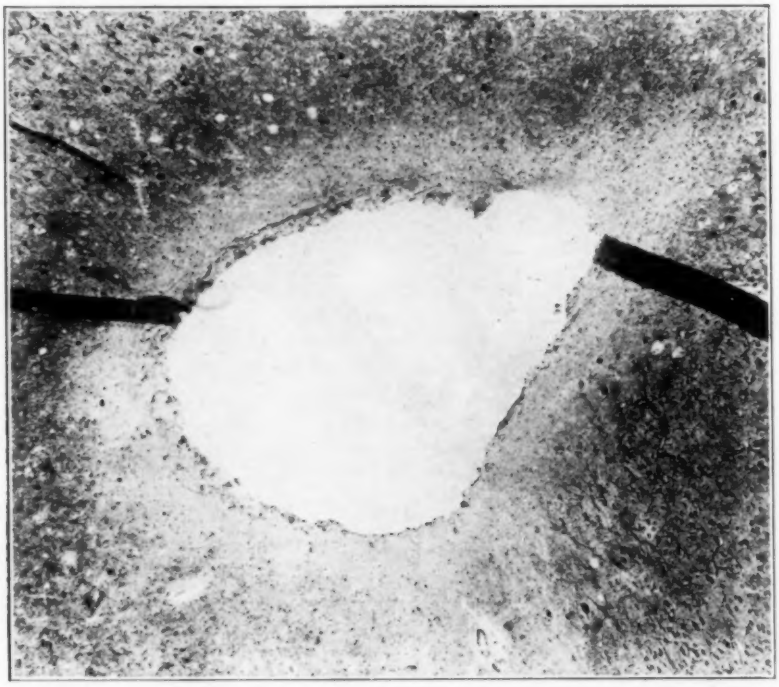

Fig. 4.—Empty track following puncture made with the hollow needle; seventy-nine days; no gliosis in the white matter.

PATHOLOGIC EXAMINATION

Examination of the gross specimens brought out the following facts: There were adhesions of the dura at the site of puncture. These were more delicate and much more easily separated on the side of the puncture made by the open needle than on the side of that made by the blunt needle. Into the tracks made by the open needle a slight amount of loose connective tissue extended downward from the dura a distance of less than 1 mm. Beneath that, each track was empty throughout its entirety in both gray and white matter in the seven cases, that is, in twenty-one tracks (fig. 1 *a*). Two small mural strands of

grayish white tissue were seen in two cases. The lining of the empty tracks was smooth and shining. Gross evidence of increased vascularity about them was not present.

On the other hand, in each of the wounds made by the blunt needle the dura was firmly adherent to the brain about the end of the track, and connective tissue passed down into each track (figs. 1 *b*, 1 *c* and 2).

Fig. 5.—Empty track following puncture made with hollow needle; thirty-one days; gliosis in cortical gray matter, no gliosis in white matter.

When the meninges were pulled on at autopsy, a distortion of the underlying brain was produced, and a connective tissue core adherent to the meninges could be dragged out. When, however, the brain was removed intact and the track made by a blunt needle cut through at right angles, it was either partially or completely filled with a connective tissue core (fig. 3). The core was loosely formed and gray-white with streaks of red suggesting small vessels. When the center

was pulled on, a definite distortion of the adjacent tissue of the brain was made. All of the cores were surrounded by a dark red zone (about 0.5 mm. in thickness) of brain tissue which was distinct from the adjacent brain tissue, and in which an increase in blood vessels could be seen with the hand lens. In the lower few millimeters of these tracks made by a blunt needle, the core was partially deficient, and an unfilled space was left. This was the case in nine of twenty-one of these tracks.

A. Open Cannula Stabs.—Microscopic examination of sections of the brain containing tracks made by an open cannula showed an empty

Fig. 6.—Higher power of cortical gray matter seen in figure 5 showing the normal arrangement of the astrocytes except near the empty track (*T*) where they group themselves in a plane tangential to the margin.

hole in the cerebral tissue in each case (figs. 4 and 5). This opening was as large or a little larger than the bore of the cannula employed. Unless specific glia stains were used, nothing unusual was seen in the surrounding brain, and there was no noticeable increase in the vascularity of the margin except when the track approaches the pia. Here there was some increase in the pial vessels.

During the early stages following the infliction of the wound, scattered compound granular corpuscles were seen close to the margins of the track. These phagocytic cells were less numerous than those about

the tracks to be described and were confined to the immediate borders of the wound. They were increased in number when a small portion of the core was left behind. In such areas the track, though still open, was sometimes lined with a layer of loosely arranged connective tissue, and in this loose layer were compound granular corpuscles and blood vessels from the surrounding brain. No true lining membrane, in the usual sense of the term, was formed.

Fig. 7.—Edge of empty track (*T*) showing the arrangement of the fibrous astrocytes; higher power of figure 6.

If the neuroglia astrocytes were stained selectively, a remarkably constant reaction was seen. Moderate gliosis was always present in the cortical gray matter adjacent to the empty tracks (figs. 4 and 5), but it did not occur about such a track in the white matter (figs. 4 and 5). In fact, the astrocytes of the adjacent white matter appeared to be definitely decreased in some cases; thus gliosis was seen only close

Fig. 8.—Connective tissue core (unstained) filling a track made by a blunt nosed brain needle. Gliosis is present in the adjacent gray matter.

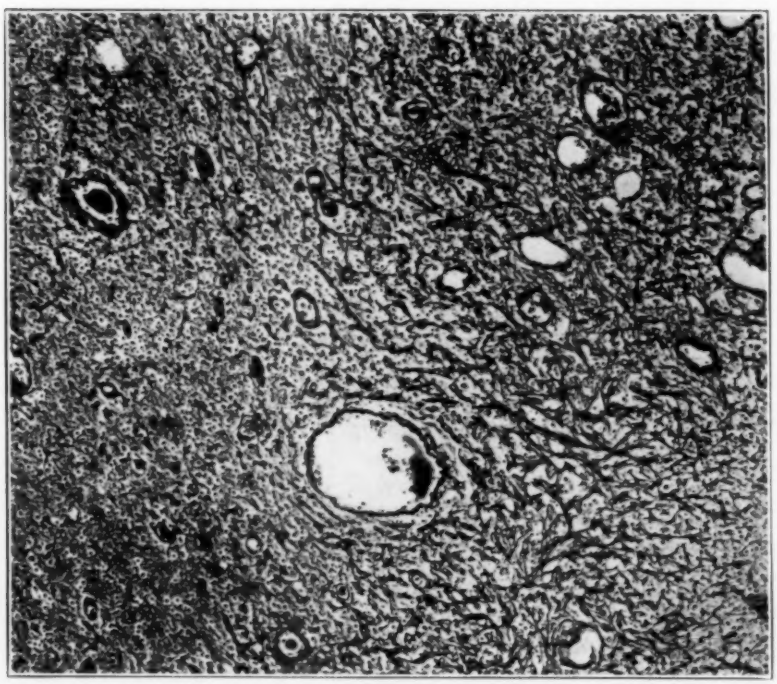

Fig. 9.—Increased vascularity in the track of a blunt brain needle two weeks after puncture. Note the new formed collagen fibers.

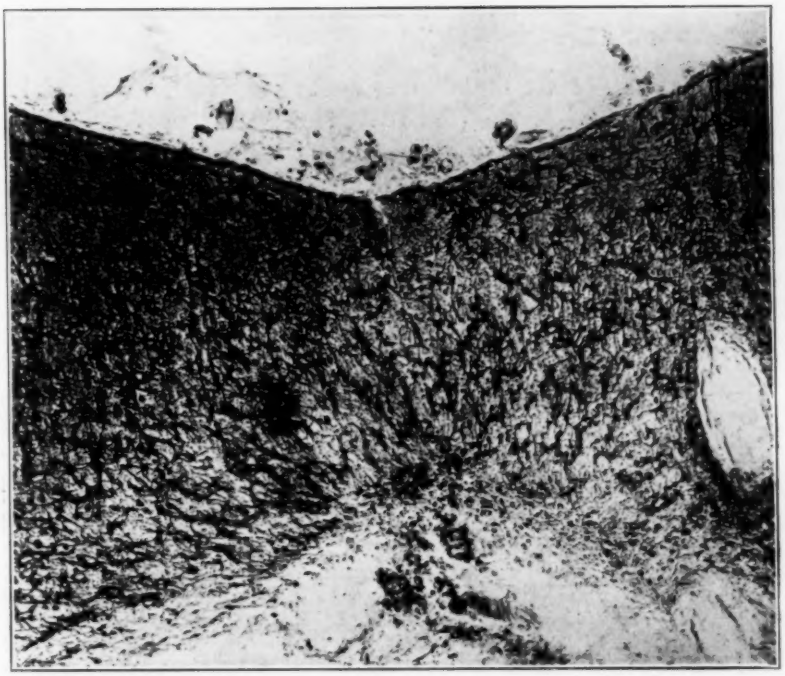

Fig. 10.—Edge of track made by puncture with blunt needle and filled with unstained connective tissue. The cortex seems to be pulled toward the track.

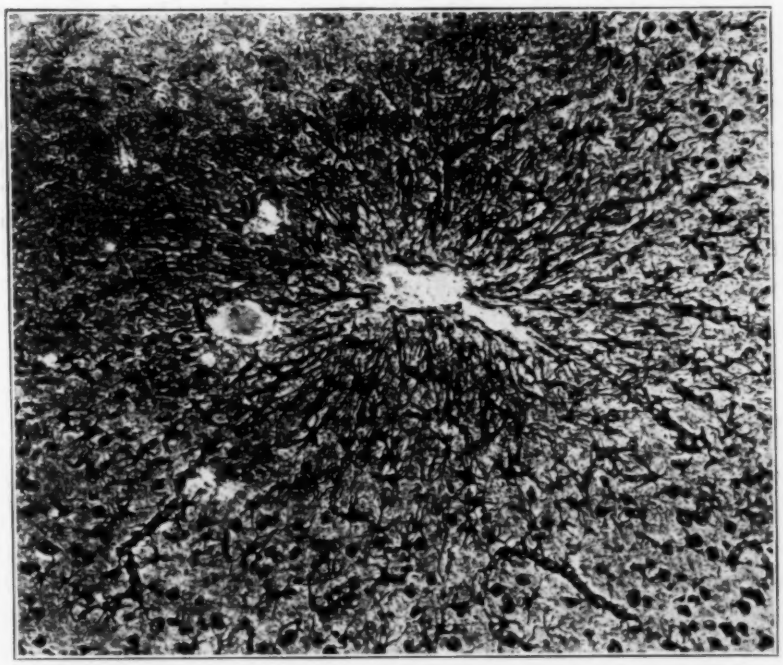

Fig. 11.—Puncture wound made by blunt needle; fibrous astrocytes radiate toward the core.

to the pia mater. Here the reacting astrocytes were fibrous and large, and they stained distinctly (fig. 6). The pattern of these cells was normal, except at the margin of the empty track where their expansions were arranged in a plane tangential to the wall of the track (figs. 6 and 7). Thus there was a matting of interlaced fibrils in the margin of the track, particularly as it passed through the gray matter.

Consequently, the outstanding features of the reaction about the open track may be said to be the absence of adhesion and contraction, a surrounding gliosis in the gray matter, lack of glial response in the white

Fig. 12.—Distortion of brain near two punctures made with the blunt needle. The connective tissue in the tracks is unstained.

matter, tangential arrangement of the astrocytes just beneath the wall of the track and absence of increase in vascularity.

B. Trocar Stabs Made with a Blunt Brain Needle.—Microscopic sections of the brain containing such tracks showed a different picture. The tracks were filled either partially or completely with cores of varying density. Close to the surface the core consisted of a close framework of thin-walled blood vessels which were seen coming from the meninges as well as jutting out from the adjoining tissue of the brain (fig. 8). They were held in a loose connective tissue framework. New-formed collagen fibers (reticulum) were numerous about these

vessels (fig. 9). Red cells may be present, and compound granular corpuscles in large numbers may be seen even as late as the seventy-ninth day after operation. The reaction in adjacent cerebral tissue includes destruction of neurons and the new formation of many small vessels. The vascular reaction seems to be as marked in the white as in the gray matter.

With selective stains a dense gliosis was seen in the cortical gray matter and little reaction of the astrocytes in the white matter. The response in the gray matter differed from the gliosis seen in the same layer about hollow tracks, in that astrocytes were oriented *toward* the core (figs. 10 and 11) instead of about the track. Their processes seemed to be drawn into the edges of the core by the entering blood vessels.

As already mentioned, the lower ends of even these trocar stabs were sometimes partially empty, in which case they resembled the tracks made by a hollow cannula. At the surface, connective tissue, continuous with the overlying dura mater, entered the track (fig. 8).

About each of the trocar tracks there was evidence of distortion of the adjacent brain. This distortion was most marked in the gray matter. It consisted in a thinning of the cortical gray with a definite pulling of the cortex toward the track (fig. 12). Hypertrophied astrocytes were present in such areas of contraction (fig. 10).

WOUND VASCULARIZATION

Further experiments were performed in order to study the origin of the newly formed blood vessels in and about the stab wounds made by blunt trocar. Thin sheets of celluloid were placed over the surface of the brain in certain cases after the stab wound had been made. The celluloid separated the pia from the dura and served to prevent the passage of vessels downward from the pachymeninx except by the most devious route. A dense membrane formed beneath the celluloid, and to it was attached the core in the track.[1] Gliosis occurred beneath the celluloid as in the other cases. Obviously, in such experiments at least, the newly formed vessels are derived from the vessels of the brain and not from without.

In another series of experiments, craniotomies were performed, stab wounds were made, and at varying intervals up to thirty days the animals were killed after preliminary injection as follows:

A solution of potassium ferrocyanide, 0.5 Gm., iron ammonium citrate, 0.5 Gm., and distilled water, 100 cc., was slowly injected, under ether anesthesia, into the external carotid and internal maxillary artery of one group of animals and into the internal carotid artery of a second series. The brain was then removed and placed in 10 per cent liquor formaldehydi containing 1 per cent hydrochloric acid. The specimens either were cleared by the Spalteholz method, and paraffin sections examined unstained, or sections were stained by the hematoxylin-eosin method.

Prussian blue could be seen in the vessels reached by injection. When only the artery of supply to the dura mater was injected, dye was found in the vessels of the brain only in a small zone about the junction of regenerating dura and track. In the experiments in which the artery supply to the brain (internal carotid) was injected, gross examination showed (fig. 13) that, not only did injected dye fill the vessels at the periphery of the healing core, but the dye filled the blood vessels in the overlying adherent meninges and muscle, communicating little with the adjacent dura. Such gross examination of the injected dye gives, of course, only a general indication of blood vessels. The chief vascular supply to the scar seems to be the vessels of the pia mater which, of course, pass inward to supply the cortex and underlying white matter. As illustrated in figure 13, however, there was a dense plexus of

Fig. 13.—Track made by blunt needle with adherent meninges and muscles. The dark lines represent injected vessels, most numerous in the pia, wound track and overlying muscle. There is no injection of the vessels of the dura mater. The injection was made through the internal carotid artery intravitam.

anastomosing vessels in the overlying muscle. This newly formed vascular plexus, in both the brain and the muscle, is evidently supplied chiefly by the vessels which under normal conditions are limited to the leptomeninges and brain.

SUMMARY AND CONCLUSION

Punctures of the brain were made by a blunt brain needle in one series and by an open cannula with a rounded edge of the same caliber in another series.

When a blunt brain needle was employed, all of the injured tissue remained behind, and a closed track containing a connective tissue core firmly attached to the overlying dura resulted. The track was sur-

rounded by a moderate gliosis in the cortical gray matter, but gliosis did not occur and there was even a decrease in astrocytes in the white matter. Occasionally, the lower end of such a track was found open.

When stab wounds were made by an open cannula of equal size and a cylinder of cerebral tissue was removed, a gaping track resulted which contained little if any connective tissue and which was slightly attached to the overlying dura. The track was surrounded by a moderate gliosis in the cortical gray matter and there was no gliosis or even a decrease in astrocytes in the white matter.

These two types of wound may be contrasted as follows: About the closed tracks, the astrocytes send in their large expansions concentrically; about the open tracks, these expansions are tangential to the canal. Compound granular corpuscles are more numerous about the closed than about the open tracks. Apparently, both needles cause the same amount of hemorrhage. There is, in general, greater formation of adhesions, greater distortion and greater destruction of the brain about the tracks made by a closed needle than about the tracks made by an open needle of the same size.

As a general principle, it follows that if destroyed cerebral tissue is left in a wound in the brain, a cicatrix results containing connective tissue which contracts and causes distortion of the brain; a greater resultant gliosis also occurs. Superficial adhesions are reduced to a minimum if the damaged brain tissue is removed.

It is evident that when a cannula is employed for exploratory punctures, it provides tissue for microscopic examination and in addition gives rise to less damage to the brain than that which takes place following the use of the usual exploratory brain needle. Further, the presence of damaged brain tissue in a wound produces a contracting cicatrix, gliosis in the contiguous areas and cerebral distortion. On the other hand, clean removal of cerebral tissue results in little if any cicatrization, moderate gliosis in the gray matter and none in the white, slight superficial adhesion and practically no distortion of the brain. It would seem to be a basic principle that when injured cerebral tissue is not removed it produces a more serious pathologic condition than the clean removal of an equal amount of such tissue.

GLIA RESPONSE IN CHRONIC VASCULAR DISEASE OF THE BRAIN *

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This study is limited to a survey of the glial reactions to chronic circulatory disturbances, atherosclerosis, in the central nervous system. No attempt, however, has been made to embrace all the morphologic changes in cerebral atherosclerosis, and it is unnecessary to recapitulate and to revaluate the numerous contributions on the subject of the histopathology of this disease. Instead, the reader is referred to the more important contributions in this field of Alzheimer,[1] Binswanger,[2] Jacobsohn,[3] Oppenheim,[4] Saltykow,[5] Stransky,[6] Rio-Hortega,[7] Neuburger [8] and Kodama.[9] The purpose of this contribution is to chart the various glial elements in their numerical and morphologic modifications as revealed by modern tinctorial methods in a chronic progressive

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* Figures 1, 2, 4, 5, 6, 8 and 9 are not published in this article but will appear in the author's reprints and in the Transactions of the American Neurological Association for 1927. Figures 1, 4, 6, 8 and 9 have appeared previously in Globus and Straus: Massive Cerebral Hemorrhage, ARCH. NEUROL. & PSYCHIAT. **18**:215 (Aug.) 1927, under the numbers 2, 12, 11, 4 and 5, respectively. Figures 2 and 5 appeared in the same issue in an article by Globus on "The Cajal and Hortega Glia Staining Methods," under the numbers 4 and 2, respectively.

1. Alzheimer, A.: Die Seelenstörungen auf arteriosklerotischer Grundlage, Allg. Ztschr. f. Psychiat. **59**:695, 1902; Einiges zur pathologischen Anatomie der Geistesstörungen, ibid. **57**:597, 1900; Ueber perivasculäre Gliose, ibid. **53**:863, 1896-1897.

2. Binswanger: Arteriosklerotische Hirnerkrankung, Vers. Mittel-deutscher Psychiat. Centralbl. f. Nervenheilk. **32**:11, 1909.

3. Jacobsohn, L.: Ueber die schwere Form der Arteriosclerose des Zentralnervensystems, Arch. f. Psychiat. **27**:837, 1895.

4. Oppenheim, H.: Ueber "druesige Nekrosen" in der Grosshirnrinde, Neurol. Zentrabl. **28**:410, 1909.

5. Saltykow, S.: Heilungsvorgänge an Erweichungen, Lichtungsbezirken und Cysten des Gehirns, Arch. f. Psychiat. **41**:1053, 1906.

6. Stransky: Beitrag zur Kenntnis der Hirnrindeveränderung bei Herderscheinungen, J. f. Psychiat. u. Neurol. **25**:106, 1909.

7. Del Rio-Hortega, P.: La macroglia y su transformation en celulas en bastoncite y cuerpos granuleediposes, Trab. d. lab. de invest. biol. univ. de Madrid **18**:36, 1920.

8. Neuburger, Karl: Ueber streifenformige Erkrankungen der Grosshirnrinde bei Arteriosclerose, Ztschr. f. d. ges. Neurol. u. Psychiat. **101**:452, 1921.

9. Kodama, M.: Die regionäre Verteilung der arteriosclerotischen Veränderungen im Grosshirn, Ztschr. f. d. ges. Neurol. u. Psychiat. **102**:597, 1926.

vascular disease. The term "chronic progressive vascular disease" in itself suggests that one is not dealing with a single sharply defined morphologic picture, but with a large series of somewhat overlapping alterations among which recent pathologic changes are superimposed on various transitional stages of more ancient processes. In cerebral atherosclerosis there is, in a single disease picture, a sequence of varied pathologic events one merging into another—the more acute passing gradually into the subacute and finally into the chronic form. Because of this sequence, it is possible to reconstruct the gradual modification of the component glial elements which play a dominant rôle in this disease process.

MATERIAL AND METHODS

Material.—The material selected was carefully scrutinized, clinically and anatomically, to eliminate the possible coexistence of another disease process, inflammatory or degenerative, such as cerebral syphilis and senile dementia; it was collected so as to include, in addition to instances of a diffuse degenerative disease, examples of circumscribed lesions in the nature of softening, hemorrhage or old cysts associated with diffuse cerebral atherosclerosis. The clinical histories will not be recorded as no correlation of the clinical manifestations with the anatomic conditions is intended. In general, the clinical character of the material used may be described briefly by saying that it was obtained from cases in which the patients during life manifested signs and symptoms of generalized as well as cerebral atherosclerosis, with or without objective symptoms pointing to focalized lesions of the brain.

Methods.—The staining methods employed have been mainly the gold chloride sublimate of Cajal and the silver carbonate processes of Hortega with the modification recently described by me.[10] This has been checked up by other usual staining processes such as those of Nissl, Weigert, hematoxylin and others.

HISTOLOGIC OBSERVATIONS

With the classification of the glial components of the central nervous system as established by Cajal and his pupils now universally accepted, it is thought best to record the histologic observations under the following headings: (1) changes in the macroglia, including the protoplasmic and fibroblastic astrocytes; (2) changes in the microglia of Hortega, and (3) changes in the oligodendroglia.

Changes in the Macroglia.—There is a well defined hyperplasia of the macroglia throughout the substance of the cerebral hemispheres.

10. Globus, J. H.: The Cajal and Hortega Glia Staining Method; A New Step in the Preparation of Formaldehyde-Fixed Material, Arch. Neurol. & Psychiat. **18**:263 (Aug.) 1927.

It is diffuse but not entirely uniform and presents quantitative variations, particularly in the white matter, which is accounted for by local differences in the degenerative changes, caused by a corresponding degree in the obstruction to the blood supply. In the cerebral cortex, however, there is an added difference. Here the hyperplasia of the macroglia is particularly noticeable, because it has acquired a new character; the usual protoplasmatic astrocytes are here almost completely replaced by fibroblastic astrocytes (fig. 1). The latter are frankly hypertrophied, as observed from the wavy outlines of their processes and their obvious increase in size. Such gliosis is not an entirely new observation. However, the wide distribution and intensity of the glial proliferation, which approaches almost a degree seen in the more profound inflammatory or degenerative diseases of the brain (general paralysis or senile involution, for instance), is striking and is best appreciated when the newer glial staining methods are employed. Glial mobilization of this character is now regarded as a primary disease of the glial apparatus. In cerebral atherosclerosis, it is aroused by generalized alteration in the blood supply to the brain. It is not, as was usually considered, a purely secondary reactive phenomenon precipitated by a loss of the parenchymal structure of the brain. Schaffer [11] and Jacob [12] have already pointed out that the glial components of the central nervous system may be affected directly and primarily in acute or chronic inflammatory as well as in acute or chronic degenerative diseases of the central nervous system. In such instances, the glial apparatus may respond either by progressive and proliferative changes or by regressive and necrobiotic alterations. The nature of either reaction depends on the intensity of the causative agent, the physiologic condition of the structure attacked, as well as on the state of health of the immediate environment of that structure (Jacob).

Both primary progressive and primary regressive alterations in macroglia in involutional diseases of the brain have already been recorded, and Jacob [12] suggests that a corresponding alteration in the quantity and quality of glia may be postulated in other progressive degenerative pathologic states. The finding of such form of glia change in chronic vascular disease of the brain is therefore not unexpected, but that it should reach a degree of glial hyperplasia found in general paralysis is highly interesting (Cajal [13] and Jacob [12]). The latter

11. Schaffer, Karl: Beiträge zur Histopathologie der protoplasmatischen Neuroglia, Ztschr. f. d. ges. Neurol. u. Psychiat. **38**:85, 1918.

12. Jacob, A.: Normale und pathologische Anatomie und Histologie des Grosshirns, Leipzig, Franz Deuticke, 1927.

13. Cajal, S. R.: Beitrag zur Kenntnis der Neuroglia des Gross und Kleinhirns bei progressiver Paralyse mit einigen technischen Bemerkungen zur Silberimpregnation des pathologischen Nervengewebes, Ztschr. f. d. ges. Neurol. u. Psychiat. **100**:738, 1925.

feature may serve as a partial explanation for the occurrence of instances in which the clinical picture of advanced atherosclerosis is so much like that of general paralysis that the final diagnosis is made only by the aid of serologic tests.

In the subcortex, fibroblastic astrocytes are also noted in exceedingly large numbers (fig. 2). They show changes in individual character not unlike those seen in the fibroblastic astrocytes in the cerebral cortex. Here, however, the uniformity is still less constant, for it is in the white matter that vascular disturbances of focal character are most pronounced and local degenerative processes of the character of softening are more frequent. The latter are responsible for the variability in the glial reaction. The age and extent of such a degenerative process determine the intensity and character of the glial response, as also the form, size and state of preservation of the astrocytes.

In areas in which the blood supply is only mildly reduced, with no massive destruction or softening of brain tissue, the glial reaction is in the nature of a mild "sclerosing gliosis" replacing the slowly degenerating parenchyma (fig. 3). In such areas of parenchymal "rarefication" the sclerosing gliosis consists mainly of fibrous astrocytes which are prominent mainly by virtue of the fact that the parenchyma is "fading" (fig. 3 *B*). The glial structure, however, is equally affected by the poor vascularity, since it shows practically no proliferative tendencies and the astrocytes appear definitely atrophic. The nuclei are small and pyknotic; their dendritic processes, which are few in number, are slender and short. These areas of rarefication are recognized as lightly stained foci since there is only a fine neuroglial matrix and the astrocytes, which are small and atrophic, are few in number. Surrounding such an area, however, there is usually a wide zone of more active glial proliferation, consisting of hypertrophying fibroblastic astrocytes (fig. 3 *A*).

An entirely different picture is seen in areas directly surrounding thrombosed blood vessels. The latter are enveloped by a zone of dense glial fibrosis (fig. 4). The latter consists of Weigert's glia fibers which can be traced to large fibroblastic astrocytes as the seat of their origin (fig. 5). They bear a strong resemblance to the so-called perivascular gliosis of Alzheimer.

Of still greater interest are the alterations seen in macroglia in or about recent or old areas of encephalomalacia. In a previous publication, Globus and Strauss [14] have suggested that encephalorrhagia, of the type occurring in apoplexy is only a terminal event added to preexisting anatomic alterations in the brain in the nature of encephalo-

14. Globus, J. H., and Strauss, I.: Massive Cerebral Hemorrhage, Arch. Neurol. & Psychiat. **18**:215 (Aug.) 1927.

malacia. For this reason, the necrobiotic changes in brain tissue in the course of vascular obstruction, such as softening and hemorrhage, are much alike and may be discussed under the terms of hemorrhagic softening, or softening, depending on whether hemorrhage had or had not occurred into the area of massive necrosis. In a sketch of a typical area of hemorrhagic softening three fairly distinct zones were described:

Fig. 3.—An area of rarefication in the cerebral subcortex. The light zone (*B*) is entirely deprived of parenchyma and is replaced by atrophic astrocytes embedded in a homogeneous, somewhat fibrous matrix. (*A*) indicates a dense zone of gliosis. Hortega's silver carbonate process 1, modified; × 100.

(*a*) a zone of necrosis, the central area of softening; (*b*) an intermediate vascular zone, and (*c*) an external zone of gliosis (fig. 6).

The differences in the glial alteration in the respective zones offer a good opportunity for the study of transitional phases in the progressive and regressive changes of macroglia.

In the external zone, the zone of glial proliferation, the fibroblastic astrocytes display, in addition to the hyperplasia, advanced progressive alterations in the character of hypertrophy (fig. 7 *A*). In the intermediate vascular zone, nearer the center of disintegrating tissue, are seen the so-called monster glia cells. By the Cajal gold chloride-sublimate method they are easily identified as fibroblastic astrocytes (fig. 7 *B*). Here and there they show implantation processes attached to vessels but, in some instances, there are (fig. 7 *A*) only fragments of foot processes which are detached from cell bodies but are still adherent to vessels. Such fragments of implantation processes are described by Cajal in general paralysis, and are probably, as he suggests, a phase in the process of clasmatodendrosis (Penfield [15]).

Some of these large fibroblastic astrocytes in hematoxylin-eosin preparations often simulate the so-called ameboid cells of Alzheimer.[16] Alzheimer assigned to them the character and function of an active phagocytic wandering cell. Later investigations by Rosenthal [17] and others,[13] however, have shown them to be cells undergoing regressive changes not unlike those found by Jacob in postmortem alterations; from his observations on experimental material he regards the ameboid glia as cells in the process of necrobiosis without special biologic functions. In this study, the conclusion is also reached that the ameboid cells of Alzheimer are degenerating and disintegrating astrocytes.

The necrobiosis of the fibrous astrocytes, as shown in the advanced clasmatodendrosis of their processes and the pyknosis and karyorexis of their nuclei, becomes more apparent the closer the proximity of the astrocytes to the center of active necrosis (softening).

The regressive changes, as the astrocytes continue to manifest more advanced disintegrative alterations, are expressed in loss of the dendritic processes, rounding up of the cell body and accumulation of a moderate amount of fat in the cytoplasm (fig. 7 *D*). In this stage of disintegration, astrocytes often have been mistaken for compound granular cells, and it was erroneously assumed that compound granular cells may be derived from astrocytes. This, on careful study of material prepared by Herxheimer's fat, Hortega's silver carbonate and Cajal's gold chloride-sublimate methods, cannot be corroborated. In fact, in this material no such transitions could be detected and it is highly questionable whether such metamorphosis ever takes place.

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15. Penfield, W., and Cone, V.: Acute Swelling of Oligodendroglia, Arch. Neurol. & Psychiat. **16**:131 (Aug.) 1926.

16. Alzheimer, A.: Beitrag zur Kenntnis der Pathologie der Neuroglia, in Nissl-Alzheimer Arbeiten, 1910, vol. 2, p. 401.

17. Rosenthal, St.: Experimentelle Studien über amoeboide Umwandlung der Neuroglia, Arbeiten über die Grosshirnrinde, Jena, 1913, vol. 6, p. 89.

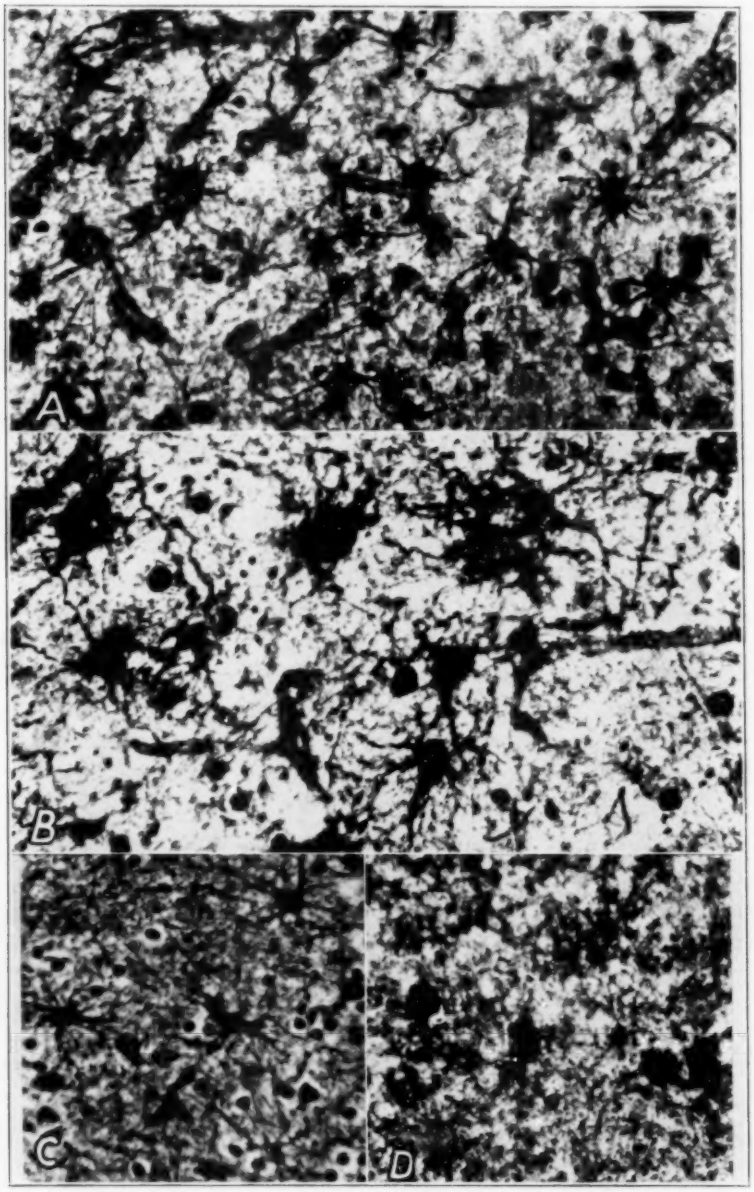

Fig. 7.—Glial changes in the wall of a recent hemorrhagic area of softening. *A* indicates a zone of gliosis, well preserved, hypertrophic fibrous astrocytes, × 300; *B*, vascular zone, monster astrocytes, swollen and undergoing partial disintegration, × 250; *C*, further breaking down of astrocytes; early clasmatodendrosis, × 215; *D*, zone of softening: degenerated astrocytes, complete loss of processes, rounding up of the cell body. Cajal's gold chloride sublimate method, modified; × 100.

In older areas of softening, in which the débris was completely absorbed leaving behind a cystic cavity, the three original zones were still discerned. The innermost is represented by a hyalinized necrotic band, while the intermediate vascular zone now assumes the character of "glial sclerosis" of the atrophic variety with regressive changes well marked in the fibroblastic astrocytes. The outer zone displays pronounced hyperplasia and hypertrophy of the fibroblastic astrocytes (figs. 8 and 9).

Fig. 10.—An old cyst, showing a hyalinized fine membrane (*H M*) with a wide zone of dense gliosis; *G*, the glia elements are exclusively hypertrophic fibroblastic astrocytes. Cajal's gold chloride sublimate method, modified; × 130.

Further advances in the organization of such cystic cavities lead to the disappearance of the intermediate zone; a thin hyaline internal membrane and a wide zone of gliosis, consisting of fibroblastic astrocytes, now form the wall of the cyst (fig. 10). Only occasionally is there an apparent attempt on the part of the fibroblastic glia to bridge over a small cystic cavity, but it is seldom complete (fig. 11). If successful, it forms a true glial scar.

Changes in Microglia of Hortega.—Many contributions have been made recently, notably by Metz and Spatz,[18] Penfield,[19] and Cajal,[13] which substantiate the observations of Hortega [7] on the so-called microglia. Among German neuropathologists there is a tendency to term this type of cell by the name of the discoverer (Hortega Zelle), which not only does justice to Hortega, but helps to identify the cell more definitely and rescues it from a terminologic confusion with mesoglia,

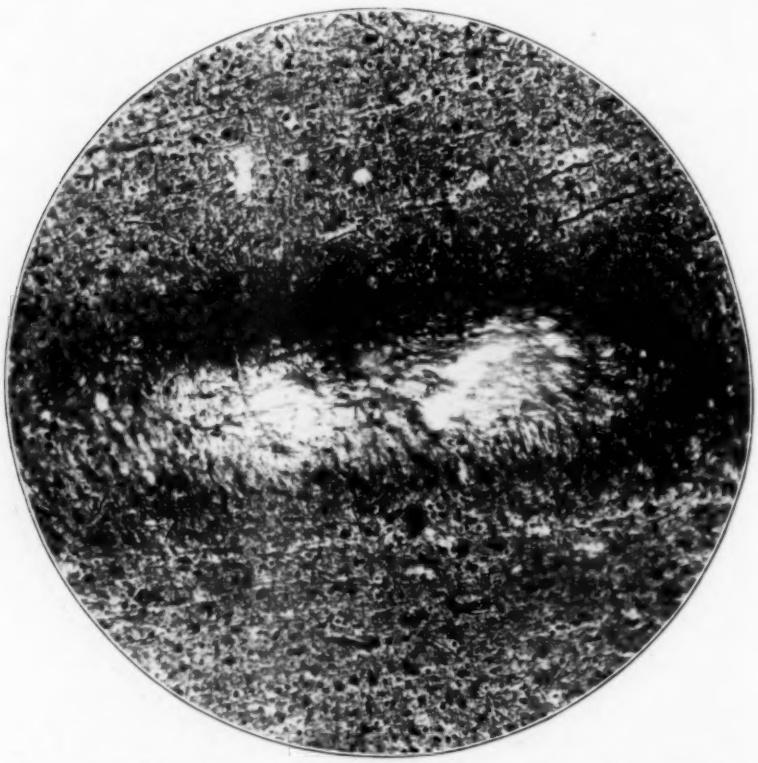

Fig. 11.—An incomplete glial scar, fibrous astrocytes bridging over a small cystic area. Hortega's silver carbonate process, modified; × 120.

interstitial glia of Achucarro, the "third element" of Cajal and the microglia of Hortega, all names designating the same cell structure, all struggling for recognition. For a detailed description of the normal microglia the reader is referred to the article by Penfield. Its morphologic and numerical as well as local variations in cerebral arteriosclerosis is of prime interest here. In material in which focal destructive

18. Metz, D., and Spatz, H.: Die Hortegaschen Zellen, Ztschr. f. d. ges. Neurol. u. Psychiat. **89**:138, 1924.

19. Penfield, W.: Oligodendroglia and Its Relation to Classical Neuroglia, Brain **47**:430, 1924.

processes are not present there is a uniform increase of the microglia. It is, however, not as marked as described by Cajal in general paralysis, but it is more pronounced than found by Creutzfeldt and Metz [20] in their material, which included cerebral atherosclerosis. The changes in the individual microglia show only slight swelling of the perinuclear protoplasm and slight hypertrophy of the processes (fig. 14 *C*).

Much more striking is the presence of aggregations of microglia in well circumscribed, small, roset-like structures. The latter are irregularly distributed and occur in the gray as well as in the white matter; more frequently in the former as single isolated nodules or in groups of from two to four in a given area. They are not unlike the so-called senile plaques (fig. 12). The latter have long been known to consist of aggregations of glia. More recently, Creutzfeldt and Metz,[20] Metz [21] and Timmer [22] have studied the plaques in senile dementia by the silver carbonate methods and have found them to be aggregations of the microglia of Hortega. A theory was advanced by Timmer [22] that senile plaques are formed in locations in which toxic agents attack selectively the substance of the brain. At such points, mobilization of microglia takes place. The latter in the course of its phagocytic activity falls victim to the assimilated toxic and catabolic products with the result that there is further proliferation of microglia with a similar fate. As the microglia degenerate, astrocytes are being attracted for reparative purposes. They are not affected by the noxious substance and remain intact. This is given as the reason why other investigators (Loewenberg [23]) have been led to assume that astrocytes play the important rôle in the construction of a plaque. These plaques of microglia bear also a strong resemblance to the so-called miliary necrosis described by Schob,[24] in which again Hortega cells, described by him as rod cells, have been found to participate actively. Rod cells, or the "Stäbchenzellen" of Nissl and Alzheimer, which were at one time regarded as pathognomonic of general paralysis, have now been definitely identified as microglia (Achuccaro,[25] Hortega,[7] Cajal [18]). They are also probably

20. Creutzfeldt, H. G., and Metz, D.: Ueber Gestalt und Tätigkeit der Hortegazellen bei pathologischen Vorgängen, Ztschr. f. d. ges. Neurol. u. Psychiat. **106**:18, 1926.

21. Metz, D.: Ueber die Bewegungsfähigkeit der Hortegazellen, Zentralbl. f. d. ges. Neurol. u. Psychiat. **43**:8, 1926.

22. Timmer, A. P.: Der Anteil der Mikroglia und Makroglia am Aufbau der senilen Plaques, Ztschr. f. d. ges. Neurol. u. Psychiat. **98**:43, 1925.

23. Loewenberg, K.: Zur Histopathologie und Histogenese der senilen Plaques, Ztschr. f. d. ges. Neurol. u. Psychiat. **95**:549, 1925.

24. Schob, F.: Ueber miliäre Nekrosen und Abszesse in der Hirnrinde eines Paralytikers, Ztschr. f. d. ges. Neurol. u. Psychiat. **95**:588, 1922.

25. Achucarro, N.: Zur Kenntniss der pathologischen Histologie des Zentralnervensystems bei Tollwut, in Nissl: Histologische und pathologische Arbeiten über die Grosshirnrinde, Jena, 1910, vol. 3, p. 143.

of a nature similar to the "Strauchwerk" of Spielmeyer [26], which is a peculiar glial reaction found in the cerebellum in typhus and other acute inflammatory diseases.

It is interesting to note that in two conditions such as senile dementia and diffuse cerebral atherosclerosis, which are often difficult to separate clinically, there is a histologic structure which was at one time regarded as pathognomonic of one (senile dementia).

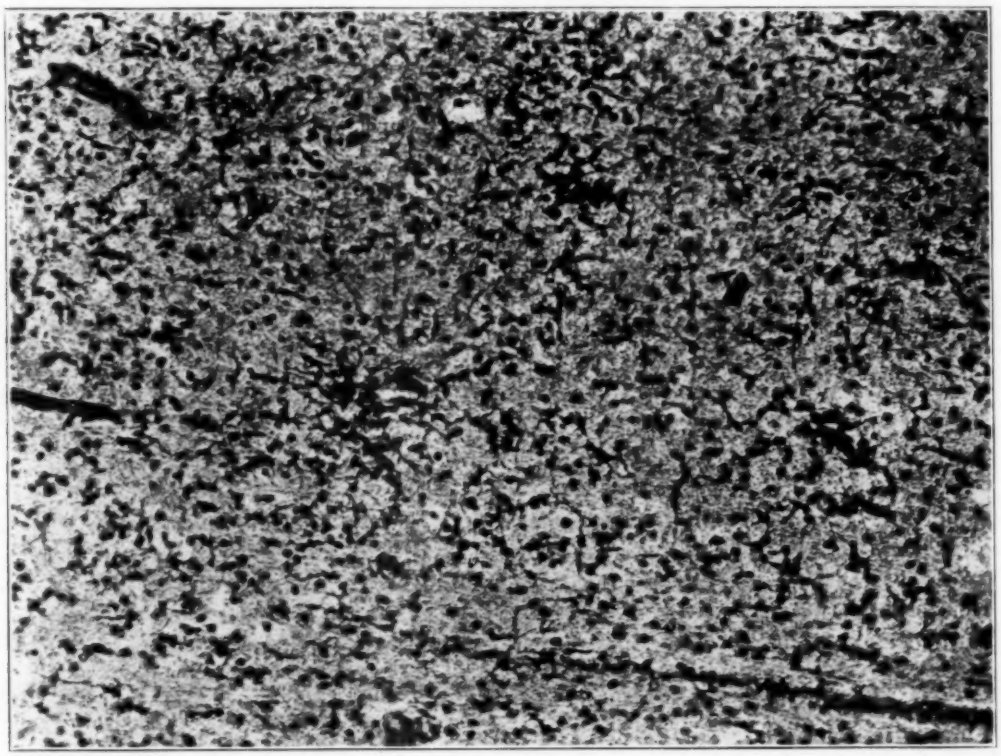

Fig. 12.—Microglia plaques not unlike senile plaques. They are roset-like aggregations of microglia. Microglia cells are also seen in large number throughout the field (see also figure 14 *A, B*). Hortega's silver carbonate process 3, modified; × 190.

The individual cells in these plaques show marked deviations from the normal appearance of the Hortega cells. Their perinuclear protoplasm is markedly increased in volume, the processes are shortened and tuberous, showing irregular, brushlike terminations. The perinuclear

26. Spielmeyer, W.: Ueber einige Beziehungen zwischen Ganglienzellenveränderungen und gliösen Erscheinungen, besonders am Kleinhirn, Ztschr. f. d. ges. Neurol. u. Psychiat. **54**:1, 1920.

protoplasm as well as the processes show fenestration and vacuolization. Some of them acquire a superficial resemblance to astrocytes, but they do not contain fibers, show a greater irregularity in the processes, do not have implantation feet, and the nuclei are neither elongated nor bilobulated (Cajal,[13] fig. 14 *A* and *B*).

Such aggregations of microglia are not in every instance an expression of neuronophagia, as believed by many, but are more often the result of alterations in the smaller components or terminal branches of the vascular apparatus of the brain. This is well illustrated by the

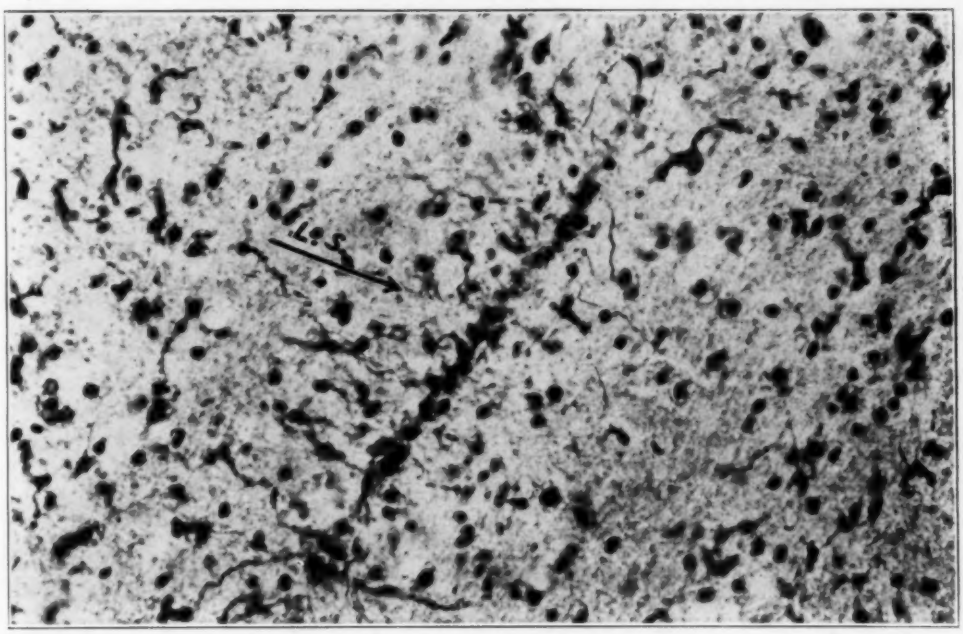

Fig. 13.—Linear microglia scar (*L S*). The scar is an aggregation of microglia along a small blood vessel. Hortega's silver carbonate process 3, modified; × 200.

linear microglia scar (fig. 13), in which one sees aggregations of microglia in the course of a small arteriole. It may be regarded as a longitudinal tangential section of a microglia plaque.

The microglial alterations are still more pronounced as areas with greater vascular disturbances are approached. In close proximity to an area of softening, and particularly in or about the vascular zone of such an area, the mobilization of Hortega cells is most active. Here, in its grouping, the microglia assumes the character of a germinal center in which Hortega cells proliferate and undergo various alterations, assuming in large numbers the type of giant microglia. They present many

transitional phases in the course of formation of the so-called compound granular cells (gitter cells), so that the latter can be traced unmistakably in their histogenesis to the so-called microglia of Hortega. Hortega [7] himself has already shown that compound granular cells are

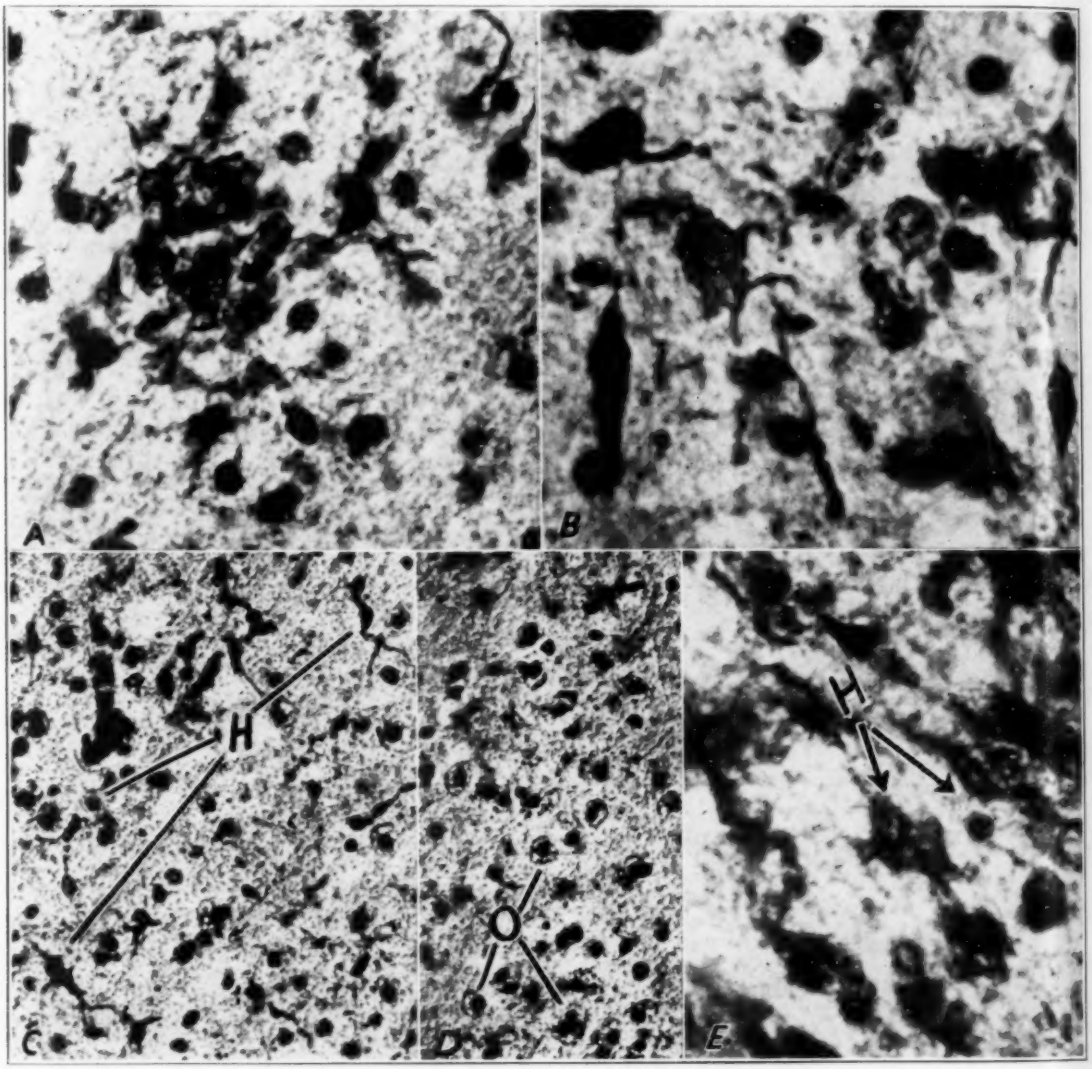

Fig. 14.—*A* indicates a microglia plaque, × 520; *B*, individual microglia cells of a microglia plaque, × 700; *C*, individual microglia (*H*) free in the field, × 280; *D*, hypertrophied oligodendroglia (*O*) free in the field, × 300; *E*, character of microglia (*H*) in a germinal center (see figure 15), × 520. Hortega's silver carbonate process 3, modified.

derived from microglia, and he is corroborated by other observers (Metz and Spatz,[18] Pruijs,[27] Penfield,[28] Creutzfeldt and Metz [20]).

When studying the transition of microglia into compound granular cells around progressive areas of softening, it is necessary to distinguish the gitter cell formation on the outer side of the vascular zone (fig. 16) from the compound granular cells found in the internal necrotic area. The origin of the gitter cells in the latter locality is still undetermined, and their possible mesodermal origin cannot be entirely disregarded, since Michels and Globus [29] studying the nature of adventitial infiltration in inflammatory lesions of the brain were able to trace the formation of typical gitter cells to migrating lymphocytes. The compound granular cells on the outer side of the vascular zone, if studied in sections stained for fat by the Herxheimer scharlach R method, are seen loaded with

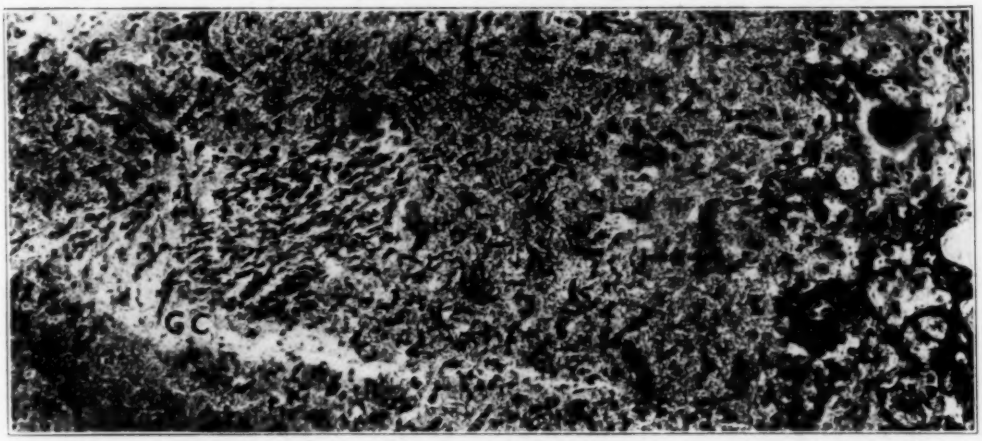

Fig. 15.—Wall of recent area of hemorrhagic softening, showing microglia-germinal center (*G C*). Hortega's silver carbonate process 3, modified; × 100.

fat (fig. 17) and show many stages in the transformation from a microglia cell of fairly normal outline to a rounded compound granular cell. These stages may be reconstructed by studying the series of cell units which were selected and cut out from the print of the photomicrograph (fig. 17) and numbered 15 to 23 (fig. 19). Such transitional forms are seen still better in a successful Hortega silver carbonate prepa-

27. Pruijs, W. W.: Ueber Mikroglia—ihre Herkunft, Funktion und ihre Verhältnis zu anderen Gliaelementen, Ztschr. f. d. ges. Neurol. u. Psychiat. **108**:298, 1927.

28. Penfield, W.: Phagocytic Activity of Microglia in the Central Nervous System, Proc. of the New York Path. Soc. **25**:71, 1925.

29. Michels, N., and Globus, J. H.: The So-Called Small Round Cell Infiltrations; ± Polio-Encephalitis and Acute Epidemic Encephalitis, Arch. Path. **4**:692 (Nov.) 1927.

ration (fig. 18). By comparing cell units in this illustration with those in the reconstructed illustration (fig. 19) it is easy to follow all the various phases in the metamorphosis of a Hortega cell into a compound granular cell. Swelling of the perinuclear protoplasm is accompanied by shortening and decrease in the number of processes; the latter become widened and vacuolated, and the vacuolization becomes more pronounced with the increase in the size of the cell. The latter now acquires the character of the so-called giant microglia cell (Cajal,[13] Hortega,[7] and Metz [21]). Regressive changes follow, and the dendritic

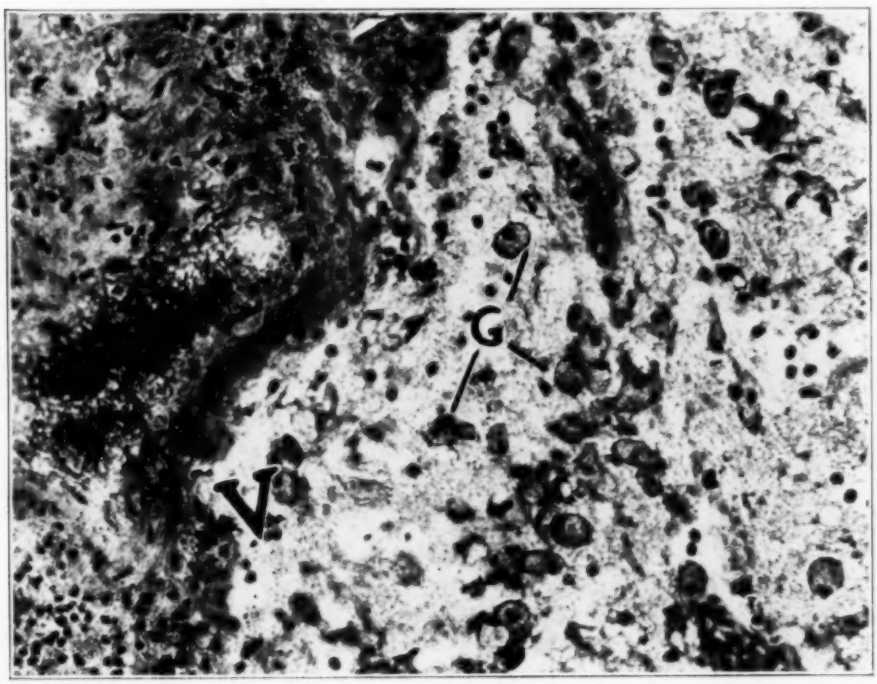

Fig. 16.—Wall of recent hemorrhagic softening showing accumulation of gitter cells (*G*) on the outer side of the vascular barrier (*V*). Hortega's silver carbonate process 1, modified; × 240.

processes are still more shortened and finally lost. The perinuclear protoplasm increases in volume, begins to become rounded and finally assumes the character of the compound granular cells.

In areas in which the microglia is in a state of active proliferation, the impression is obtained that the cells are also migrating from a germinal center to a point of active necrobiosis. This is in agreement with Hortega's conception of the wandering capacities of microglia, but is objected to by Metz,[21] who is unable to recognize migrating activity in

microglia, and thinks that the apparent migration in local mobilization of microglia is merely an expression of more active growth at the periphery of a germinal center.

CHANGES IN OLIGODENDROGLIA

The most uniform alteration in this form of glia is seen mainly in moderate swelling. This is widely distributed, and it would seem that not a single cell of this type escaped this change. There seems also to be a definite and marked increase in the number of the oligodendrog-

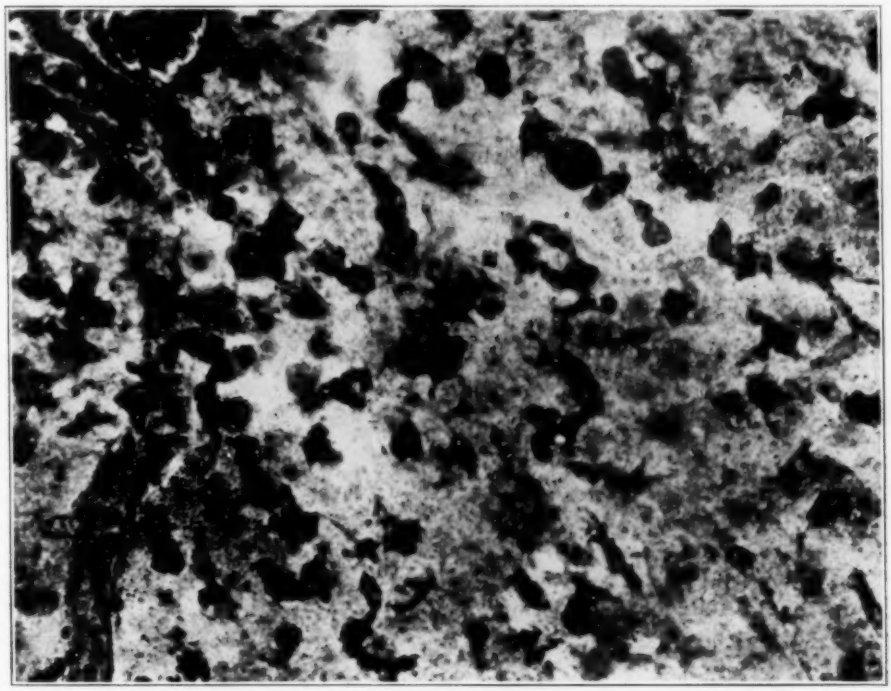

Fig. 17.—Wall of recent area of hemorrhagic softening showing mobilization of microglia transforming into gitter cells. Herxheimer scarlet R and hematoxylin; × 250.

lia cells (fig. 14 *D*). This may be more apparent than real, because the hypertrophy makes them conspicuous. It is striking that when the necrobiotic process is at its height, there are comparatively few oligodendroglia cells. Beyond this, no other oligodendroglia alterations, including those described by Penfield and Cone,[15] are observed; neither are the observations of Pruijs [27] that oligodendroglia may give rise to compound granular cells corroborated by careful study of this material. It is true that a moderate amount of fat is found in this form of glia

as it is found also in astrocytes, but, as already shown by Struwe,[30] it is never in such a large amount as is found in the microglia.

SUMMARY

The glial alterations in cerebral atherosclerosis bear out observations of other investigators on the morphologic and pathologic properties of the three main glia types.

The changes in protoplasmatic and fibroblastic astrocytes are in the nature of a primary affection of the glial apparatus. Progressive changes

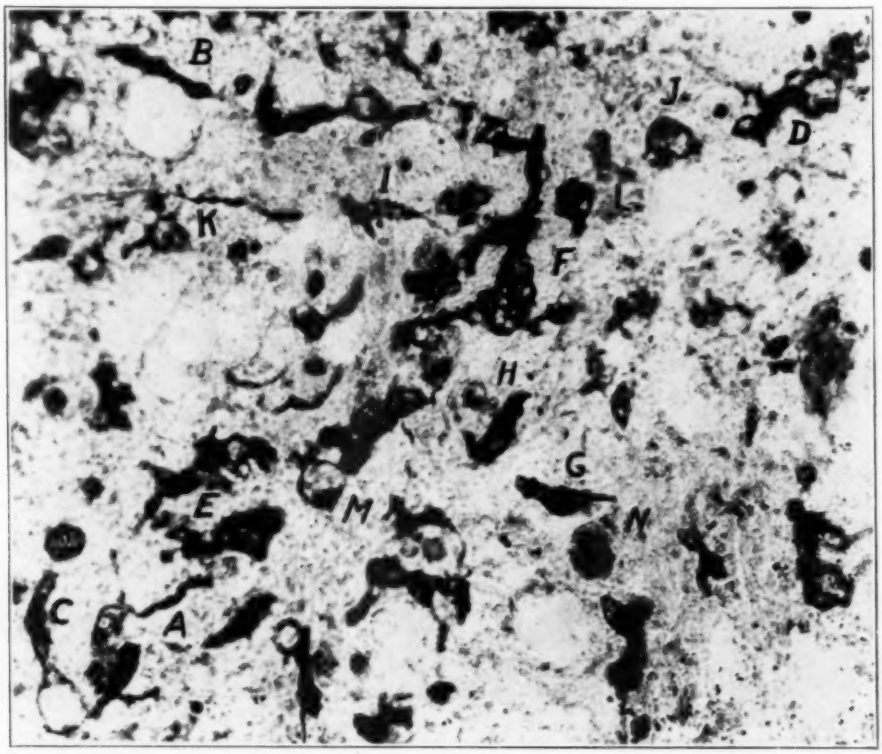

Fig. 18.—Wall of recent area of hemorrhagic softening; vascular zone in which microglia undergoes transformation into gitter cells. (Compare with figure 19.) Hortega's silver carbonate process 3, modified; × 600.

are almost universal and are expressed in generalized hyperplasia and hypertrophy of astrocytes with the conversion of the protoplasmatic type into the fibroblastic variety. The hyperplasia is apparently in direct response to a mild but generalized nutritional disturbance. In

30. Struwe, F.: Ueber die Fettspeicherung der drei Gliaarten, Ztschr. f. d. ges. Neurol. u. Psychiat. **100**:450, 1925-1926.

areas in which obstruction to blood supply reaches greater proportions, however, there occurs fibroblastic gliosis of an intensity in accordance with the degree of this disturbance. Thus mild "sclerosing gliosis" occurs in areas of parenchymal rarefication in partially ischemic zones, or rapidly regressive changes with the gradual breakdown of the astrocytes. The latter, in the course of disintegration, going through various regressive phases such as clasmatodendrosis, rounding up of the cell

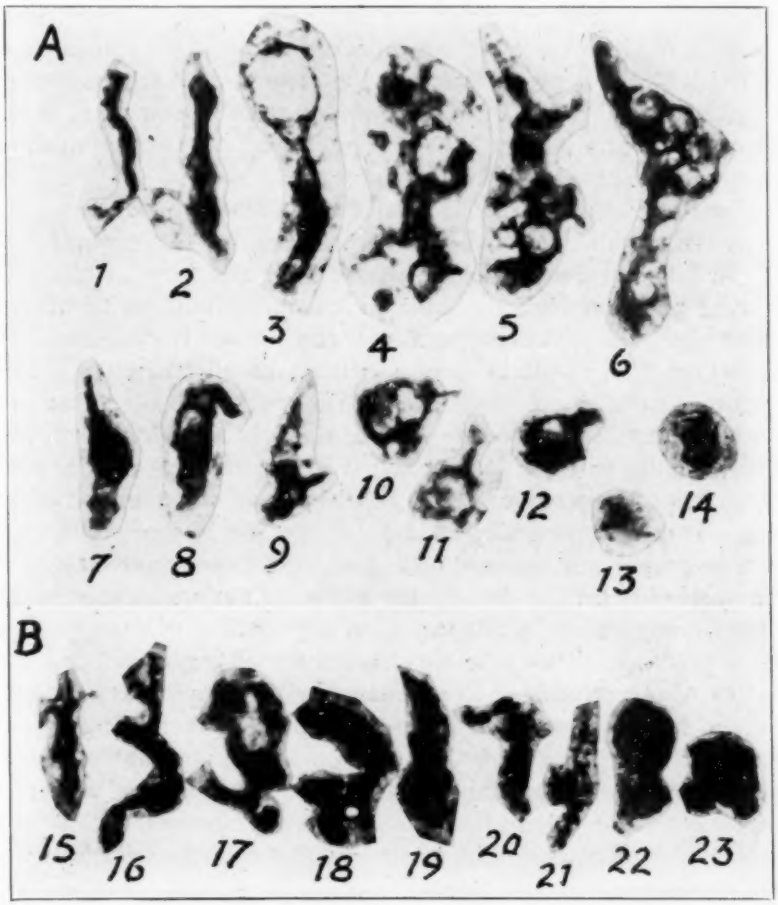

Fig. 19.—*A*, cell structures numbered 1 to 14 are figures cut from the print of a photomicrograph (fig. 18) showing phases in transition of microglia into compound granular cells; 1 to 6, hypertrophy and vacuolization of processes; 7 to 14, regressive changes leading to gitter cell formation. *B*, cell structures numbered 15 to 23 are similar changes in microglia seen in fat preparations (fig. 18). Here again microglia cells are seen in gradual transformation into gitter or compound granular cells.

body and moderate accumulation of fat particles, acquire a character strongly resembling that of the compound granular corpuscle. They do not, however, become true gitter cells, notwithstanding the claim that astrocytes contribute to the formation of these phagocytic cells.

The quantitative increase of macroglia is not characteristic of, or limited to, cerebral atherosclerosis, for it is found, even to a higher degree of hyperplasia, in other chronic inflammatory or degenerative lesions of the brain. The transformation of the protoplasmatic astrocytes into the fibrous type also is not specific for cerebral atherosclerosis, as it is found in other conditions and is described by Cajal in general paralysis. The same is true of the dense glial sclerosis around thrombosed blood vessels or in scar forming areas in which they are only an expression of a general healing or reparative process and are found wherever pronounced vessel changes occur.

More significant are the changes in the microglia of Hortega, which are also not pathognomonic of atherosclerosis. The reason for this is to be found in the physiologic character of this form of glia. This cell type plays an important rôle in the metabolic activity of nerve tissue under both normal and pathologic conditions. It stores nourishing material, and as a wandering scavenger it helps to discard waste products under many conditions. It is the type of cell which by virtue of its physiologic nature is present wherever there is need for a scavenger, for a rebuilder or for a storing cell unit. In cerebral atherosclerosis, in which the degenerative process is widespread, the need for such an element is met by generalized hyperplasia of the Hortega cells. Then again, because of the frequent occurrence of massive necrobiosis in this disease, there is further demand for a larger focal proliferative activity of the Hortega cells. In this way focal aggregations of microglia make their appearance. They take the shape either of small roset-like structures or of larger proliferative fields, so-called germinal centers, areas in which the migratory phagocytic microglia cells become transformed into gitter cells for a wider distribution in adjacent areas of active tissue destruction. These alterations again are not limited to cerebral atherosclerosis. They are found in a variety of diseases, such as senile dementia, acute inflammations (typhus) and chronic progressive inflammatory processes (general paralysis).

CONCLUSIONS

1. The glia changes in cerebral atherosclerosis are not specific for this disease. They are primary and, to some extent, secondary alterations in response to a disturbed blood supply.

2. The changes in astrocytes are mainly progressive, with generalized hyperplasia, hypertrophy and transformation of protoplasmic astrocytes into the fibroblastic variety.

3. In partially ischemic zones, the astrocytes also undergo atrophy, and in areas of softening they manifest regressive changes terminating in complete disintegration.

4 Astrocytes in the process of disintegration may assume the morphologic features of the so-called ameboid cells of Alzheimer or may simulate gitter cells; in both instances they do not gain a new physiologic significance, since ameboid cells are not a definite cell entity and astrocytes do not form true "gitter cells."

5. Hortega cells are found in large numbers throughout the substance of the brain, including the cortex and subcortex, in cerebral atherosclerosis; they generally show slight hypertrophy.

6. Hortega cells aggregate in certain circumscribed areas, forming small roset-like collections simulating senile plaques.

7. Hortega cells are mobilized in areas near localized massive destructive processes in large numbers. Here they constitute the so-called germinal centers within which they show great variability in form. A large number of them take the form of the giant microglia cell of Cajal, while others undergo regressive changes with final formation of true compound granular cells, gitter cells.

8. The changes in oligodendroglia are mainly expressed in generalized hyperplasia and mild hypertrophy. They are fewer in number or entirely lacking in areas of active necrosis.

9. The observations recorded warrant the assumption that astrocytes of both types are mainly concerned in the process of repair while the Hortega cells are essential in metabolic activity of brain tissue and are phagocytic in character; in that rôle they are responsible in large measure for the formation of compound granular corpuscles or gitter cells.

ACUTE PATHOLOGIC CHANGES IN NEUROGLIA AND IN MICROGLIA*

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NEW YORK

Understanding of the acute changes which the interstitial cells of the central nervous system undergo has increased step by step with the improvement and simplification of cytologic methods. The newer impregnation methods of Cajal[1] and Rio-Hortega[2] serve to demonstrate the pathologic alterations in the supporting cells as clearly as they show their normal histologic detail and to demonstrate them in the same selective manner. With these specific methods the acute changes which the various cell groups undergo can be followed clearly. Many questions which had to be left unanswered because of inadequate staining methods can be settled.

Much of the work on the acute changes in the interstitial cells by the Spanish school of neurology has been done with the use of experimental material from animals. It has seemed worth while to present the acute changes as they are seen in material from human beings[3] and to give the conclusions which their study indicates.

ACUTE SWELLING OF OLIGODENDROGLIA

The acute alterations in oligodendroglia have been called acute swelling because of the rapidity with which the change can occur and because swelling is the striking feature. Normal oligodendroglia from human beings resembles that seen in other mammals except that the

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* From the Departments of Surgery and Pathology of Columbia University in the Presbyterian Hospital.

1. Cajal, S. R.: Sobre un nuevo proceder de impregnación de la neuroglia y sus resultados en los centros nerviosos del hombre y animales, Trab. d. lab. de invest. biol. **2**:219, 1913; El proceder del oro-sublimado para la coloración de la neuroglia, ibid. **14**:155, 1916; Una modificación del método de Bielschowsky para la impregnación de la neuroglia común y mesoglia y algunos consegos acerca de la tecnica del orosublimado, ibid. **18**:129, 1920.

2. Del Rio-Hortega, P.: Noticia de un nuevo y fácil método para la coloración de la neuroglia y del tejido conjunctivo, Trab. d. lab. de invest. biol. **15**: 367, 1917; El tercer elemento de los centros nerviosos, Bol. d. la Soc. españ. de biol. **9**:68, 1919; Estudios sobre la neuroglia; la glia de escasas radiaciones (oligodendroglia), Bol. d. l. r. Soc. españ. d. historia natúral **10**:1, 1921.

3. All of the illustrations are photomicrographs. With the exception of figures 18 and 19, they were photographed at a magnification of × 2,000. The magnification of figure 18 is × 1,100 and that of figure 19 is × 700.

projections present larger varicosities or "knees." The normal nucleus impregnates lightly. The cytoplasm is homogeneously black or densely granular (figs. 1 and 2). As swelling occurs, the earliest change from the normal is an irregular increase in the size of the cell body. Unstained fluid pushes out the cell membrane (fig. 3). With increasing

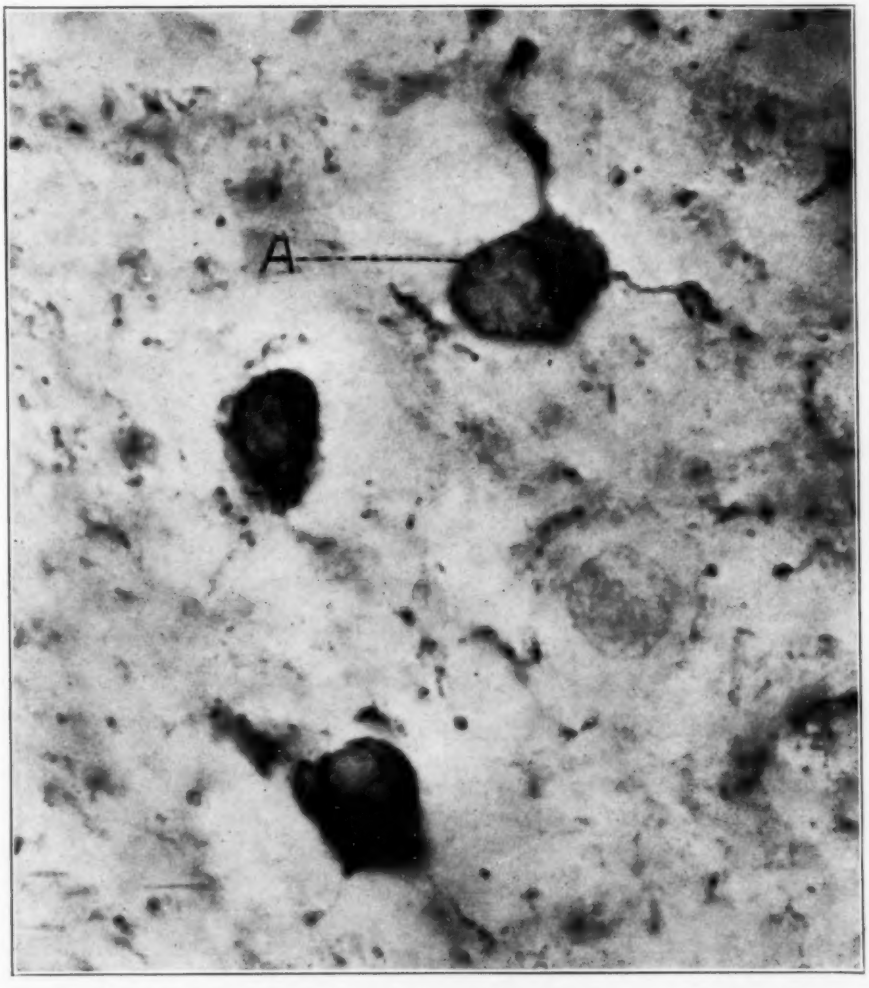

Fig. 1.—*A* indicates oligodendroglia in the gray matter. The nucleus impregnates lightly; the cytoplasm and the expansions are dark and somewhat granular. Silver carbonate stain for oligodendroglia.

swelling, granules are seen on the cell membrane, and the expansions are less numerous and are enlarged (fig. 4). Later, the expansions are indicated only by chains of granules (fig. 5). In extreme swelling, the cell body is greatly enlarged and septums or protoplasmic girders

extending from the nucleus to the cell membrane divide the body into regular vacuoles (fig. 6). Finally, the cell membrane may vanish, leaving the nucleus bare. The nuclei themselves vary considerably. In general, there is progressive shrinking and pyknosis. Because the

Fig. 2.—Normal oligodendroglia on a vessel. The projections cross the vessel but do not have vascular attachments. Silver carbonate stain for oligodendroglia.

normal nuclei of these cells impregnate lightly this reversal as swelling occurs is notable.

The acute change in oligodendroglia may take place in both the white and the gray matter of all parts of the central nervous system (figs. 7, 8 and 9). It has been found even in the optic nerve.

The contents of the large, regularly disposed, unstained spaces in the cytoplasm are not entirely clear. Stains for lipoids have given negative results. When acute swelling of oligodendroglia cells has been the only evidence of pathologic change in the central nervous system I have

Fig. 3.—Early swelling of a perivascular oligodendroglia cell. Unstained fluid has pushed the cell membrane out. Silver carbonate stain for oligodendroglia.

been unable to stain mucin in them. It has seemed that this acute change in these cells was due to hydropic swelling. Grynfeltt and Pagés,[4] however, described mucin in oligodendroglia in acute nervous diseases.

4. Grynfeltt and Pagés: Étude critique de quelques opinions nouvelles sur la dégénérescence muquese du systéme nerveux, Bull. Soc. sc. méd. et biol. de Montpellier et du Languedoc Méditerranéen **7**:210, 1925.

Bailey and Schaltenbrand [5] likewise report having stained mucin in the swollen oligodendroglia cells of a patient with periaxial encephalitis.

Oligodendroglia, by its acute swelling, may be the only group of interstitial cells to show change. In the sections from all parts of the

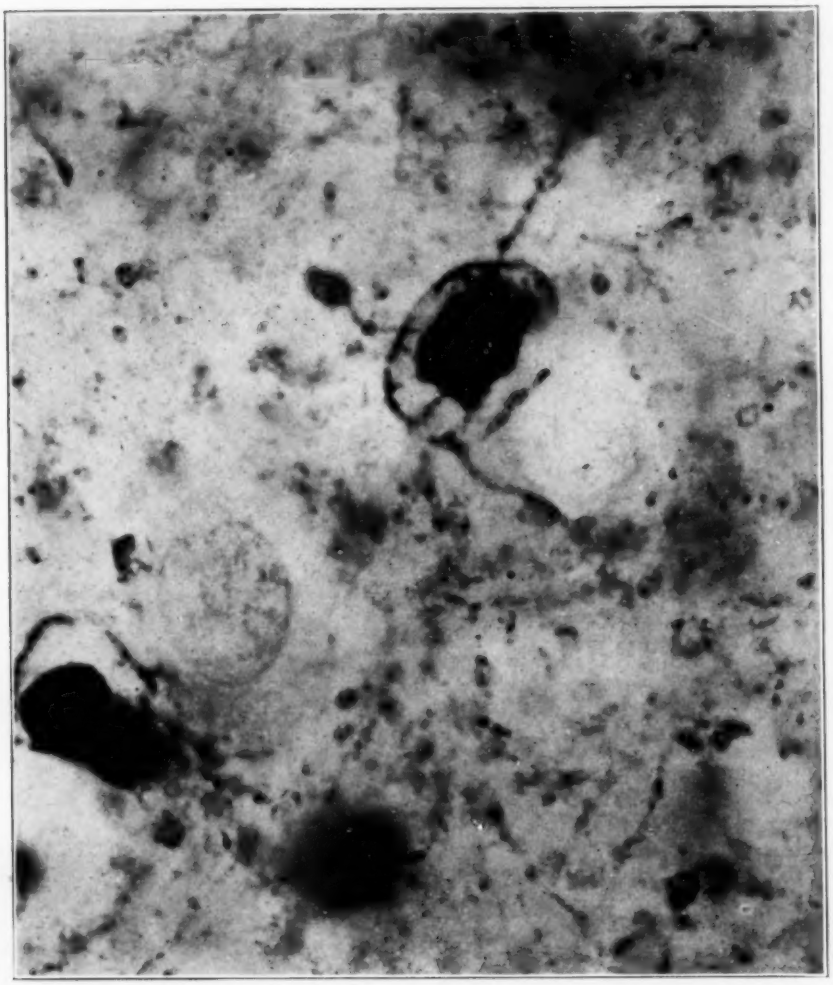

Fig. 4.—Swollen oligodendroglia cell in the gray matter. The protoplasmic projections are still seen and the varicosities they present are enlarged. Silver carbonate stain for oligodendroglia.

central nervous system in the cases in which the photographs of figure 10 were taken, astrocytes and microglia were normal. Oligodendroglia alone showed demonstrable alterations. This is not unusual.

5. Bailey, P., und Schaltenbrand, G.: Die muköse Degeneration der Oligodendroglia, Deutsche Ztschr. f. Nervenh. **97**:231, 1927.

However, when extreme acute swelling of oligodendroglia was present, astrocytes also always showed some evidence of an acute change. Moreover, in all instances in which astrocytes showed any acute change, oligodendroglia always showed marked swelling.

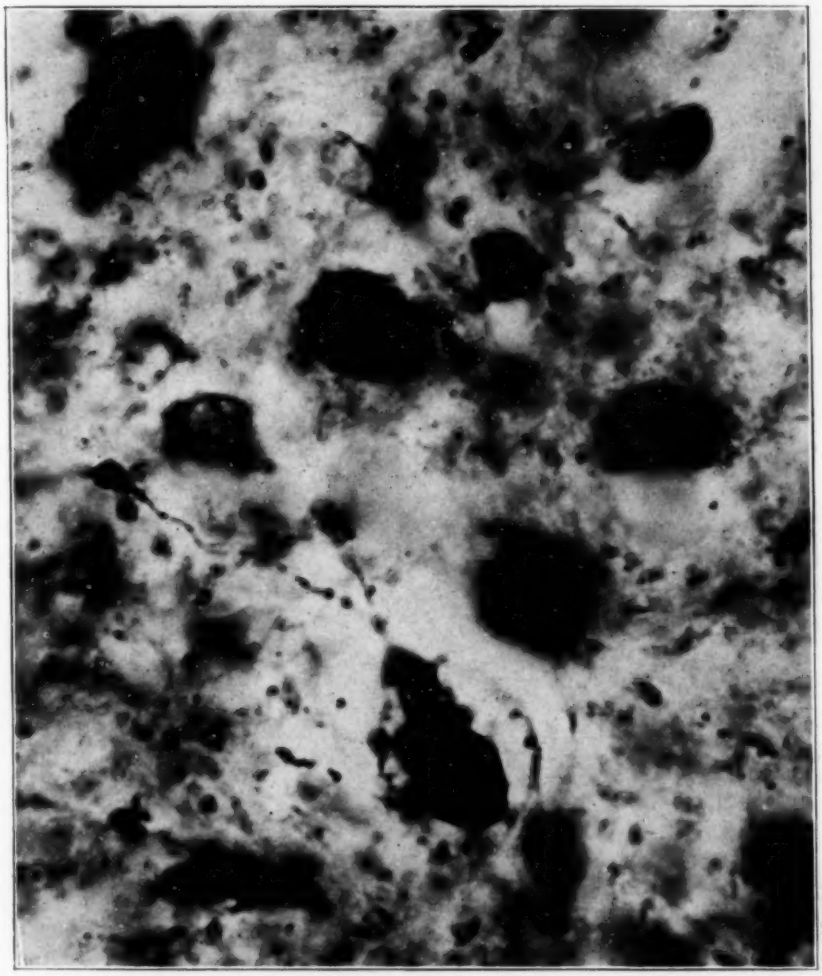

Fig. 5.—Swollen oligodendroglia cell in the white matter. The course of former projections is now indicated by chains of granules. Silver carbonate stain for oligodendroglia.

This acute change in the small round cells forming the interfascicular glia and the majority of the perineuronal satellites was first described in its entirety by Penfield and Cone.[6] However, it had been demon-

6. Penfield, W., and Cone, W.: A Specific Type of Neuroglia Change; Acute Swelling of Oligodendroglia, Arch. Neurol. & Psychiat. **16**:131 (Aug.) 1926.

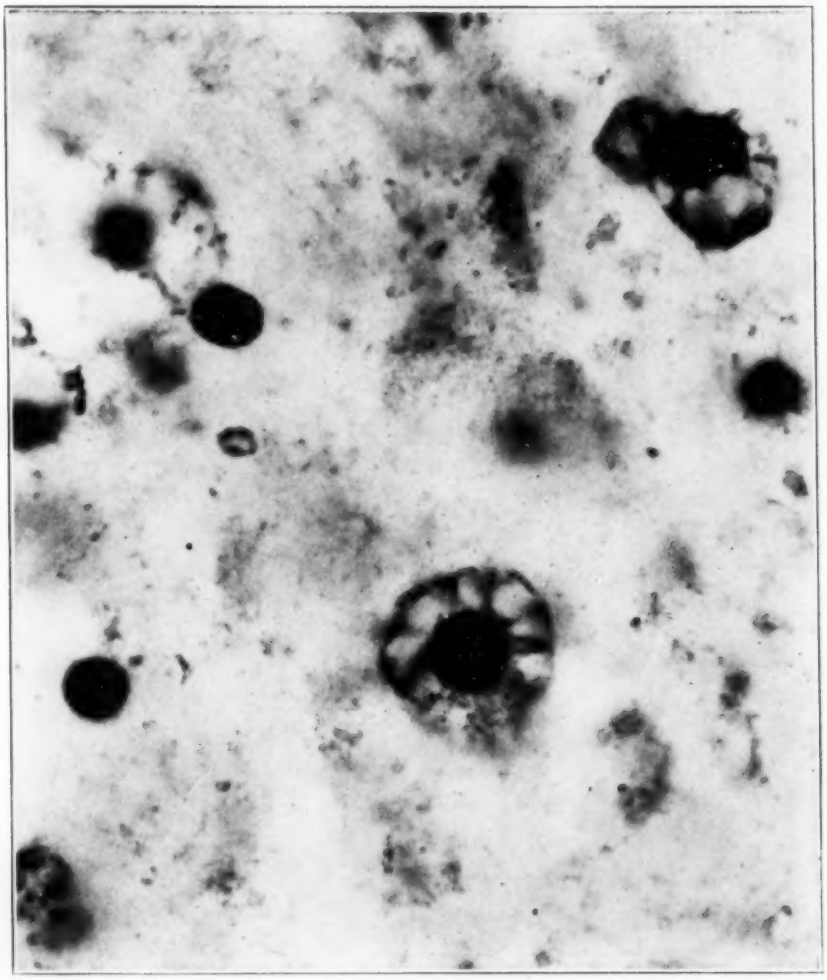

Fig. 6.—Extreme swelling of oligodendroglia. The protoplasmic expansions have disappeared. The nucleus impregnates densely, is small and is centrally placed, septums which divide the unimpregnated protoplasm into vacuoles radiate out from the nucleus "as spokes radiate from the hub to the tire of a wheel." The cell membrane is distinct, and granules are present on it. Silver carbonate stain for oligodendroglia.

strated incompletely by Alzheimer [7] and his students. Alzheimer realized he was not staining these cells with all their parts. He pointed out that they were altered in the acute diseases of the central nervous system, and added that because of their number they required careful consideration. He termed the change he noted in them ameboid glia.

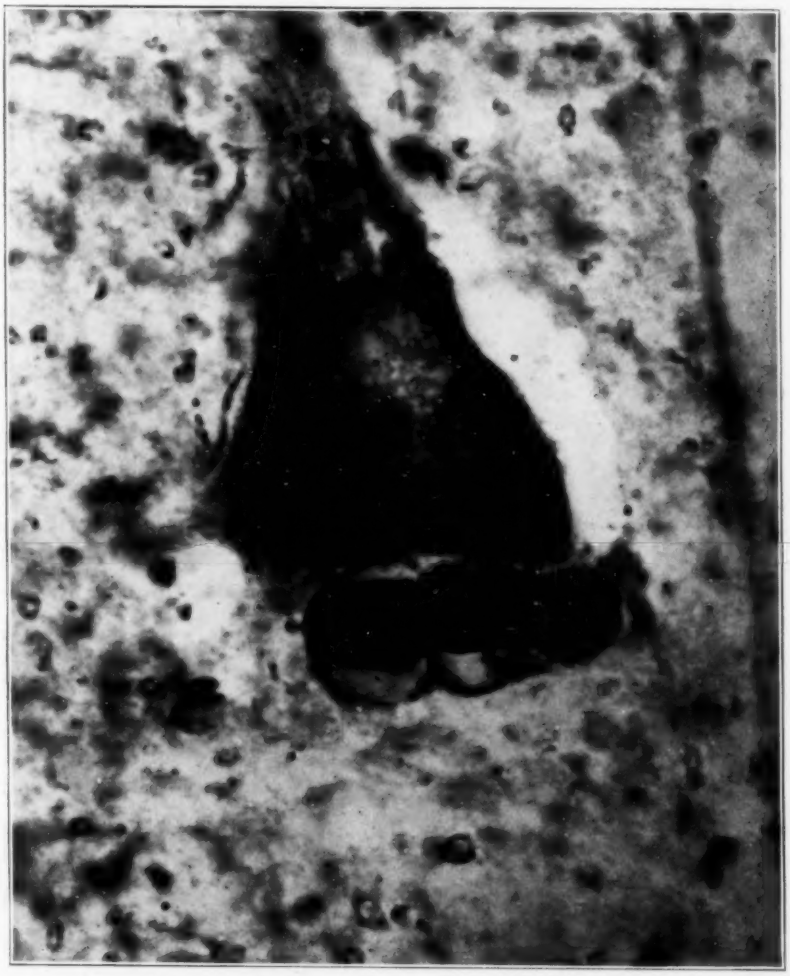

Fig. 7.—Extreme swelling of three oligodendroglia cells which are perineuronal satellites. Small granules and vacuoles representing broken up expansions are present. Silver carbonate stain for oligodendroglia.

7. Alzheimer, A.: Ueber den Abbau des Nervengewebes, Allg. Ztschr. f. Psychiat. **63**:568, 1906; Beiträge zur Kenntnis der pathologischen Neuroglia und ihrer Beziehungen zu den Abbauvorgangen im Nervengewebe, Histol. u. histopath. Arb. ü. die grosshirnrinde, Jena **3**:401, 1910.

not because they assumed the typical ameboid forms he had described in changing astrocytes, but because they contained granules of the same type that his typical ameboid glia cells presented.

Rosental,[8] too, described the reactions in the small round glia when studying experimentally intoxicated animals. He pointed out that their

Fig. 8.—Extreme swelling of the oligodendroglia cells present as perivascular satellites. Silver carbonate stain for oligodendroglia.

swelling was the first evidence of change on the part of the interstitial cells. Then, because his staining methods were not specific, he wrongly

8. Rosental, S.: Experimentelle Studien über amöboide Umwandlung der Neuroglia, Histol. u. histopath. Arb. ü. die Grosshirnrinde, Jena **6**:89, 1913.

concluded that after swelling they formed typical ameboid glia cells. He therefore called their first alteration, as shown by swelling of the cell body and pyknosis of the nucleus, a preameboid change. The value of these early observations to this study is the support they offer to it and to the observations of Penfield and Cone, made in 1925, on acute swelling of oligodendroglia. The correctness of many of the

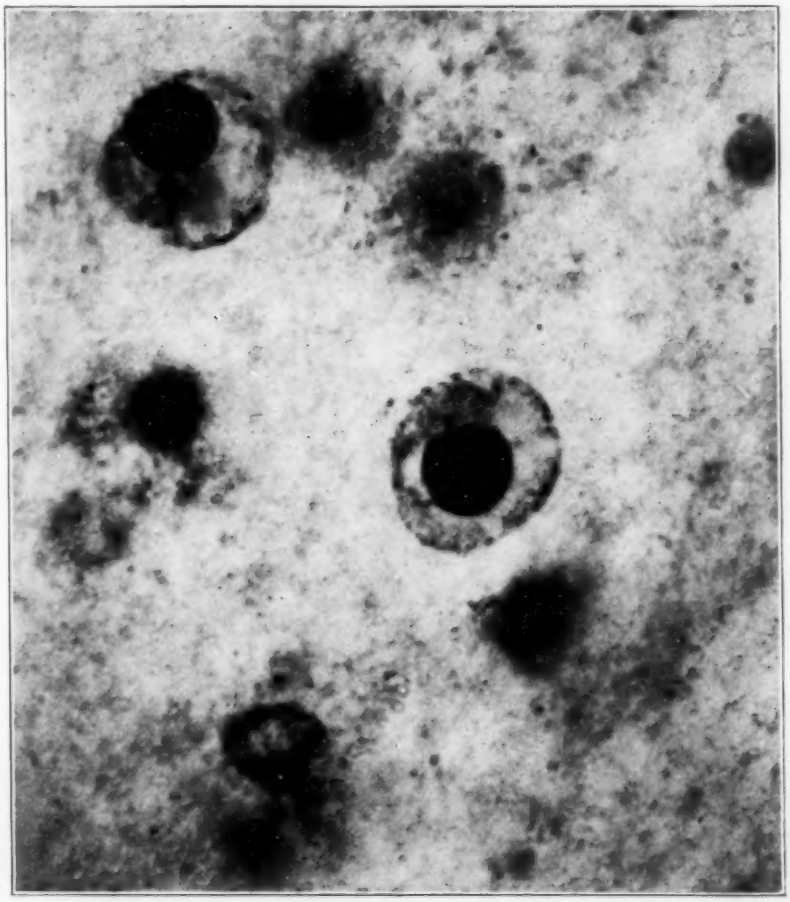

Fig. 9.—Extreme swelling of oligodendroglia in the white matter. Silver carbonate stain for oligodendroglia.

conclusions of Alzheimer and his students, though they did not have specific staining methods, shows the remarkable thoroughness and keen interpretation which mark their studies.

In the work on acute swelling of oligodendroglia, both in experimentally produced intoxications in animals and in autopsy material from human beings,[6] the following conclusions were drawn: Acute

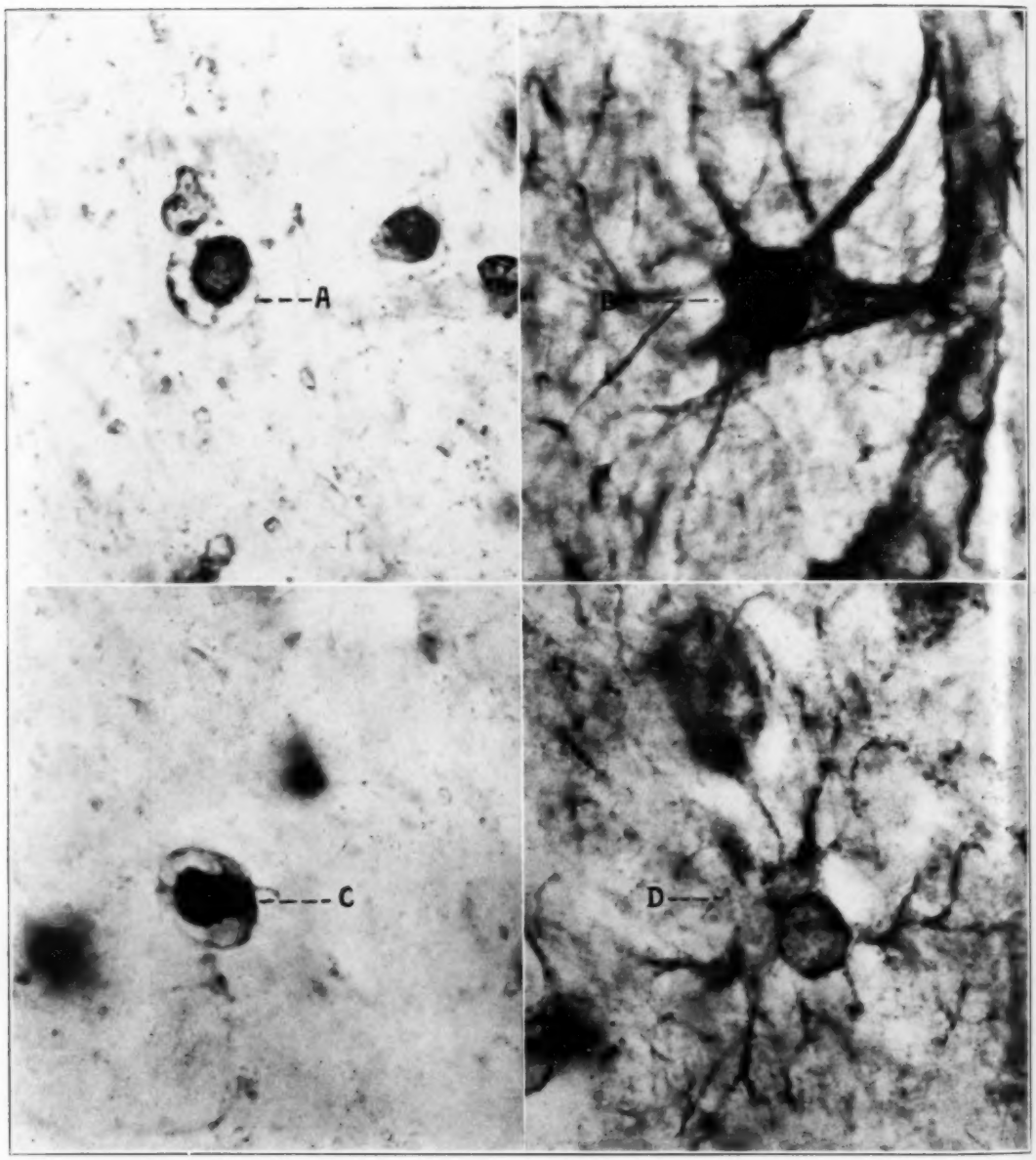

Fig. 10.—Taken from cases in which oligodendroglia was the only interstitial cell to show change: *A* indicates swollen oligodendroglia in the white matter; *B*, normal fibrous astrocytes of white matter; *C*, swollen oligodendroglia in the gray matter; *D*, normal protoplasmic astrocyte of the gray matter. Oligodendroglia stained with silver carbonate, astrocytes with Cajal's gold sublimate.

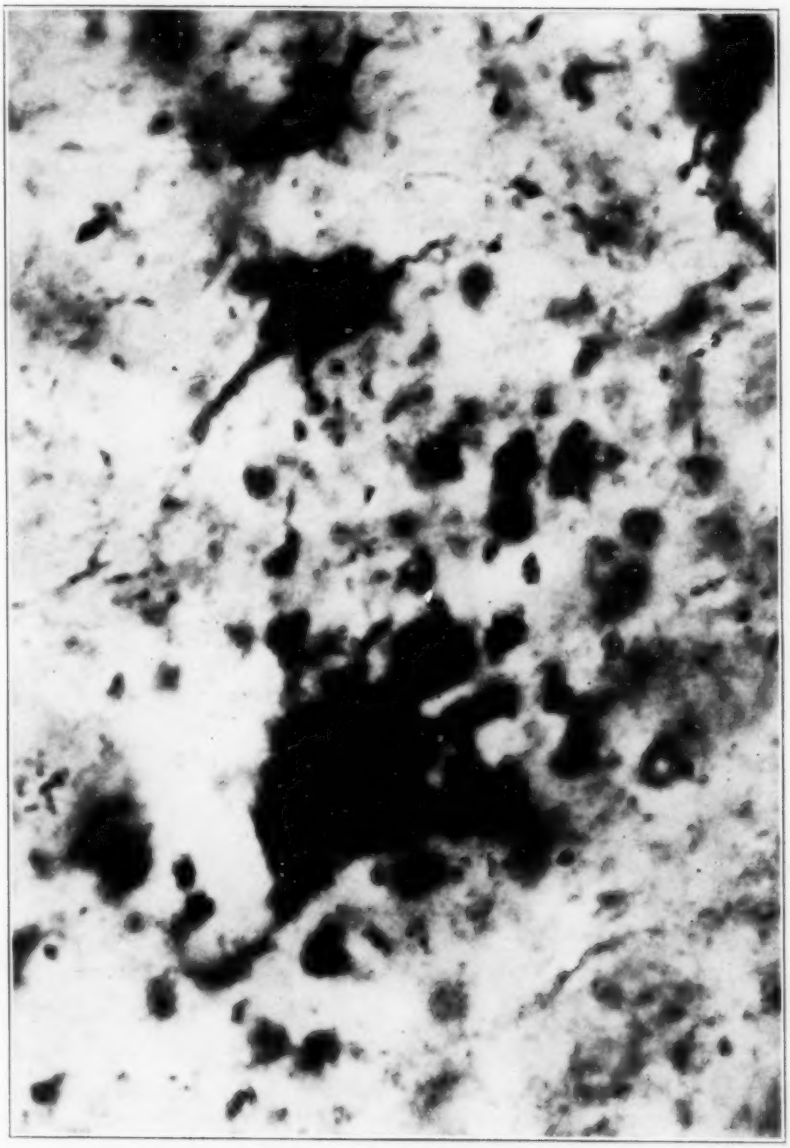

Fig. 11.—Fragmentation of neuroglia astrocyte with little swelling. This is an acute change. This fragmentation of the projections Cajal called "clasmatodendrosis." Cajal's gold sublimate stain for astrocytes.

swelling of oligodendroglia is a specific cell change which may go on to cell destruction. Throughout the change, these cells retain their specific affinity for the silver carbonate of del Rio-Hortega.[2] They never resemble in their histologic characteristics changing microglia or changing astrocytes. Acute swelling may be caused by a purely autolytic

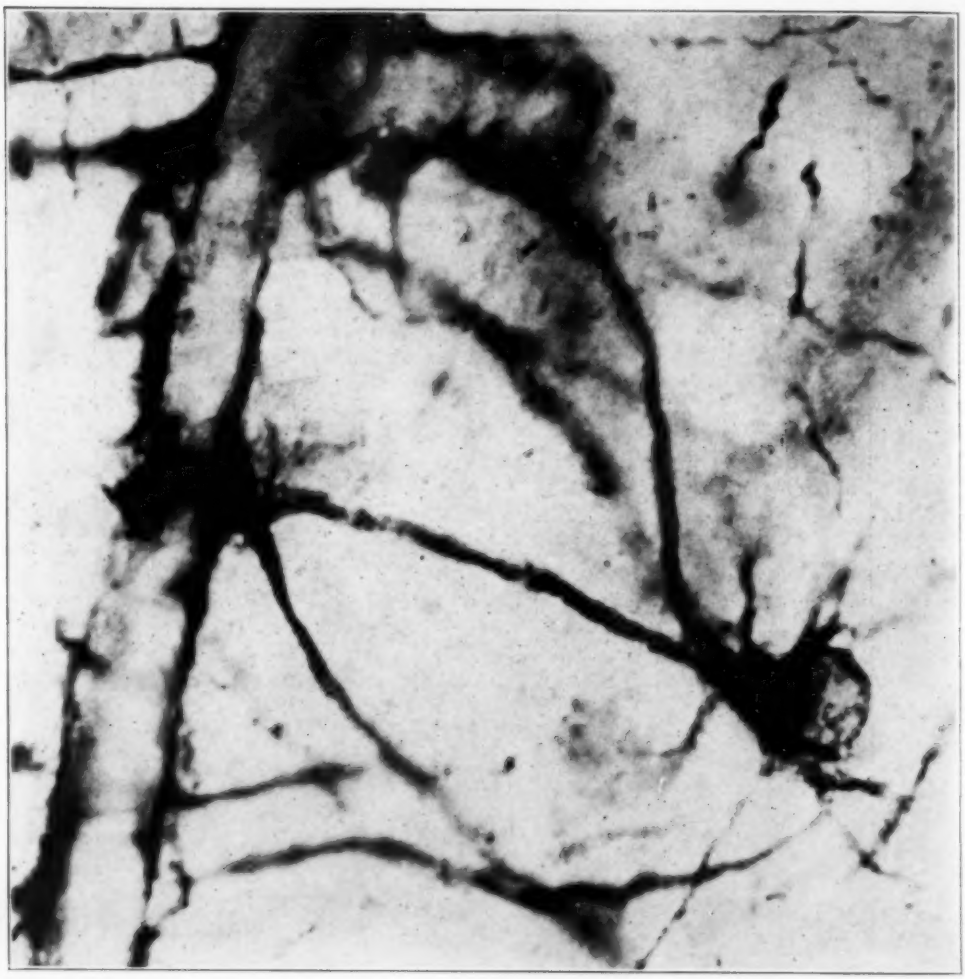

Fig. 12.—Normal young astrocyte or astroblast taken from same section as that from which figure 11 was photographed and illustrating the patchy nature of this acute change. From the brain of an infant, aged 2 months. Cajal's gold sublimate stain.

condition, but it may be found well marked during life. The cases of early autopsy in human beings which showed it were cases of toxic delirium or cases in which coma preceded death for some time.

Rosental [8] suggested that his preameboid glia change was reversible. Considerable evidence was brought out in Penfield and Cone's work to show that acute swelling of oligodendroglia was a reversible change. Further work is being done to demonstrate this theory conclusively, and added clinical cases have strengthened it.

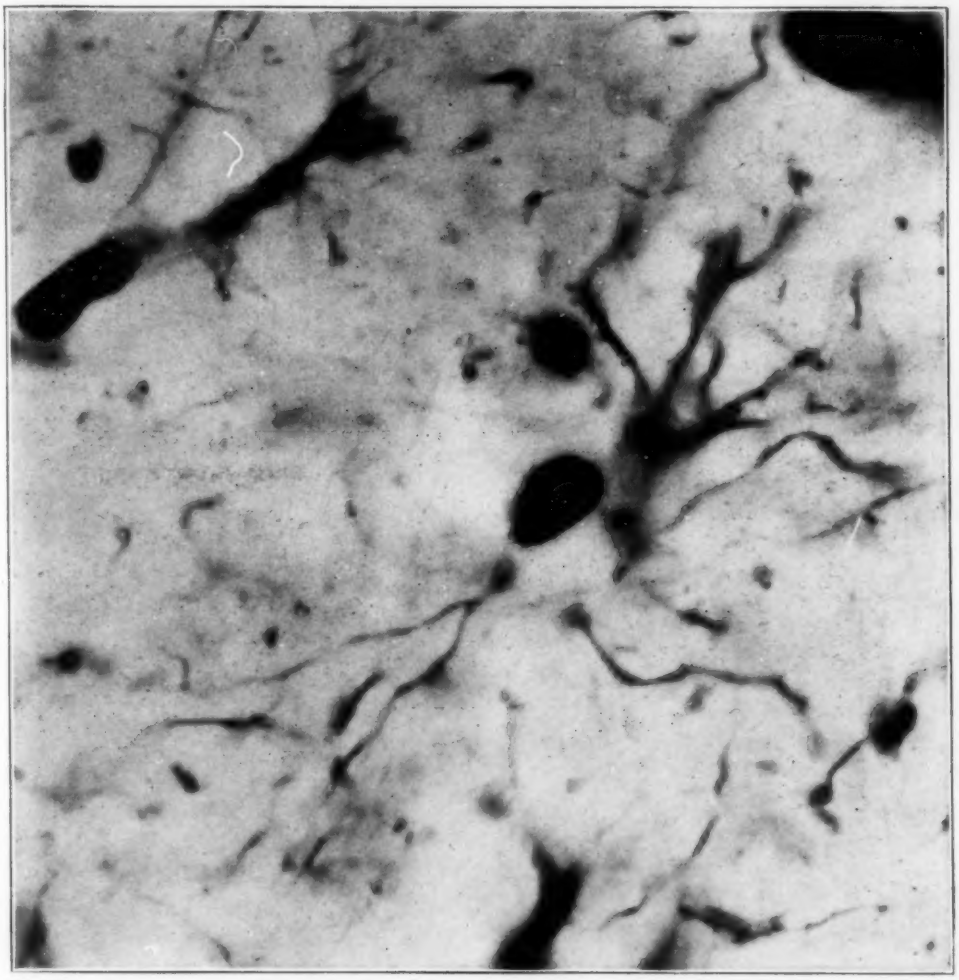

Fig. 13.—Fibrous astrocytes. The fibers have disappeared. The projections are swollen and can be followed for long distances. Moniliform swellings are present on the projections. This is one of the earliest changes toward ameboid glia. Hortega's silver carbonate astrocyte stain.

In del Rio-Hortega's experiments reported in his original description [2] of oligodendroglia, most of the work was done on animals. Some of his drawings of oligodendroglia from human beings showed

what I have described as an early stage of acute swelling. Cajal's failure to accept oligodendroglia as a specific cell group may have been due to the fact that he did not recognize the acute alterations which these cells undergo. He pictured in a recent article on the neuroglia changes in general paralysis [9] beautiful examples of extremely vacuolated

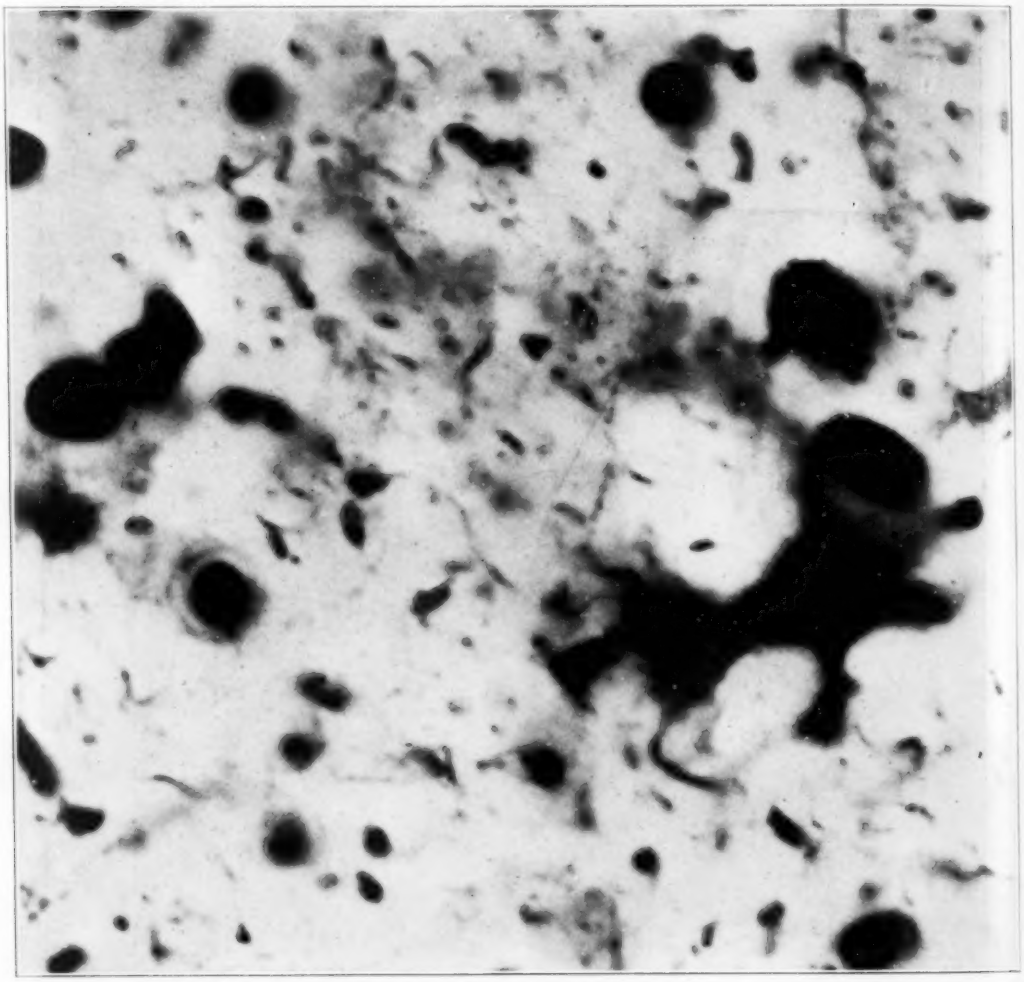

Fig. 14.—Preameboid glia of Hortega. The projections most distant from the cell have broken up; the cell body and the remaining projections are swollen. Hortega's silver carbonate astrocyte stain.

9. Cajal, S. R.: Contribution à la connaisance de la nevroglie cérébrale et cérébelleuse dans la paralysie générale progressive avec quelques indications techniques sur l'impregnation argentique du tissue nerveux pathologique, Trav. du lab. de recherches biol. de l'Univ. de Madrid **23**:157, 1925.

round cells but was unwilling to admit their relationship to the "oligodendroglia of Hortega and Penfield."

Acute swelling of oligodendroglia may be present during life. It has occasionally been found as the only evidence of pathologic change in pieces of brain removed at operation in an exploring brain needle

Fig. 15.—Ameboid glia. At this stage the swelling of the cell and its projections resembles an ameba with its pseudopodia. Hortega's silver carbonate astrocyte stain.

and fixed at once. The clinical improvement in some of the patients showing acute swelling of oligodendroglia at operation has been so great that it has seemed that the process must have been reversible.

The difficulty experienced in obtaining normal oligodendroglia from human beings may be pointed out. In routine autopsies, acute swelling was always present. Rarely, a few normal cells were found. The degree of swelling varied with the time post mortem and the clinical symptoms preceding death. The only sections in which all oligodendrog-

Fig. 16.—An ameboid glia cell surrounded by masses formed from broken up projections; these irregular and numerous bodies are the Fullkörperchen of Alzheimer. Hortega's silver carbonate astrocyte stain.

lia cells were normal were obtained either in cases of sudden death with early fixation of material or in material removed at operation and fixed immediately.

ACUTE CHANGES IN ASTROCYTES

CLASMATODENDROSIS AND AMEBOID GLIA

The most acute change which neuroglia astrocytes show with the new impregnation methods consists of a fragmentation of the expansions of the cell with little or no swelling (fig. 11). The cell body is

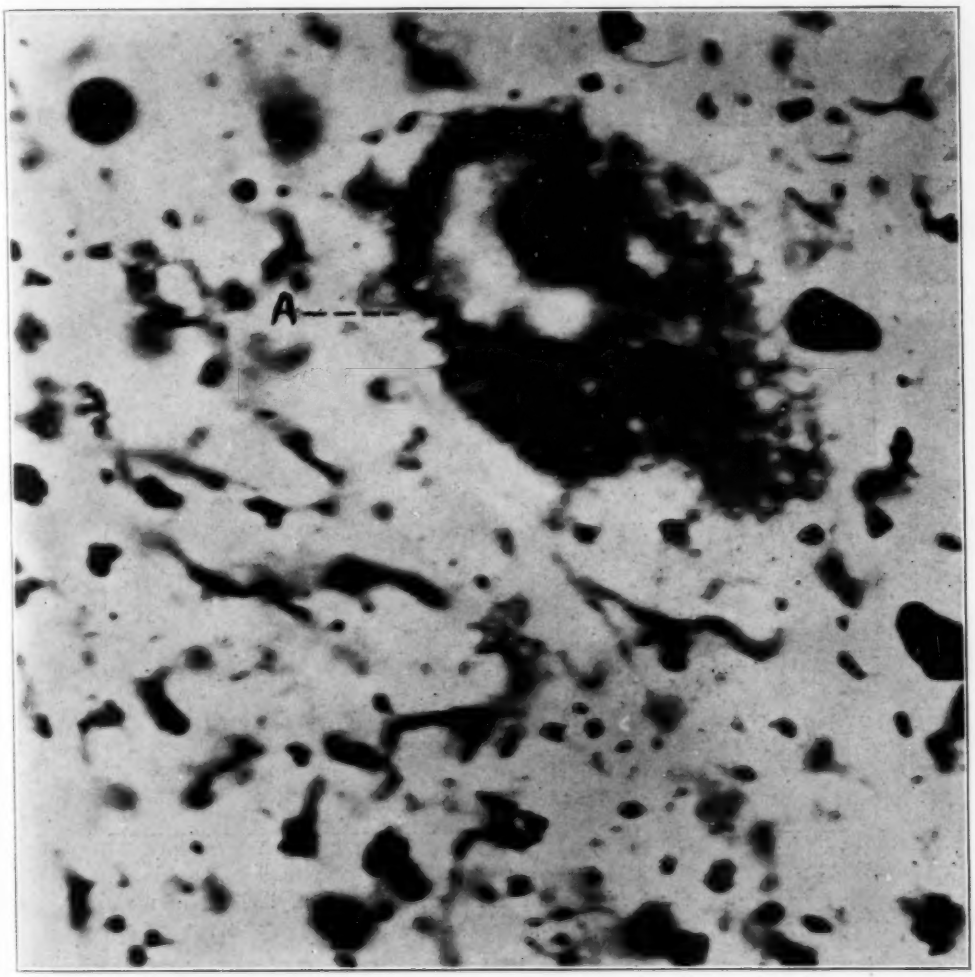

Fig. 17.—*A* indicates ameboid glia. Vacuoles and granules stand out in the cytoplasm. If Alzheimer's staining method VI is used, fuchsinophil granules and lipoid cysts can be demonstrated in the cell body of such a cell. Hortega's silver carbonate astrocyte stain.

surrounded by rows of bodies outlining the course of the former projections. Such a change is apt to be patchy, and in the sections from which the cell in figure 11 was photographed most of the astrocytes were normal (fig. 12).

A second acute change in astrocytes seems to be more gradual than that just described. It is characterized in its first stages by swelling of the cell body and hypertrophy of the projections, which impregnate densely and show moniliform swelling along their course (fig. 13). As swelling progresses, the portion of the projection most distant from the cell body breaks up (fig. 14). Finally, cell forms result which resemble amebas with their pseudopodia (figs. 15 and 16). The large bodies seen about the ameboid cells are the bodies formed by the breaking up of swollen expansions (fig. 16).

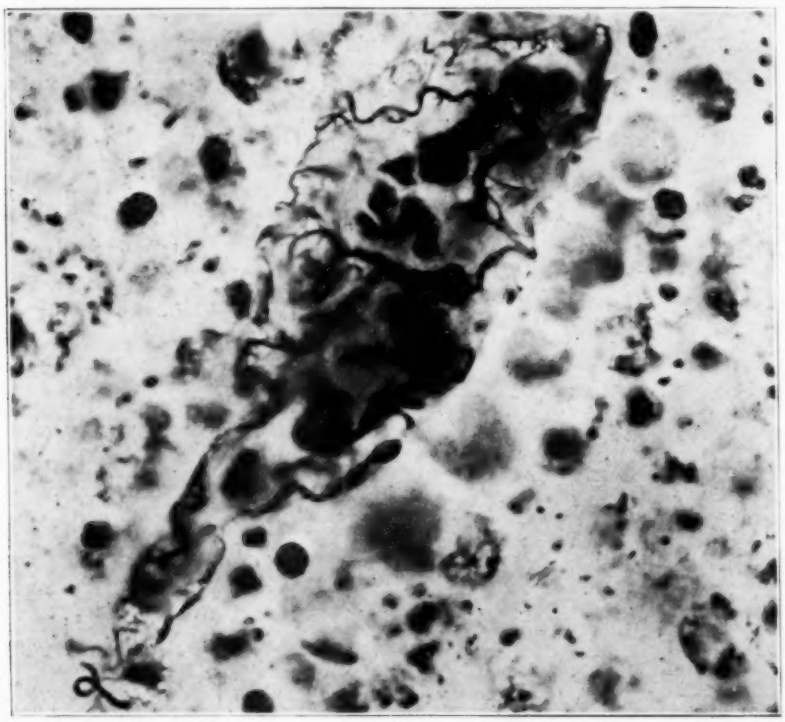

Fig. 18.—Filling bodies in the perivascular space of a vessel formed by the breaking up of the vascular feet of astrocytes. The cell bodies from which these fragmented projections came are not seen. Hortega's silver carbonate astrocyte stain.

In all stages of the acute change, the nuclear change is usually, though not invariably, pyknotic. Swelling of the cell body increases even after the expansions have broken up, when, in the cytoplasm, large granules stand out (fig. 17).

In the acute change, the vascular attachments of the astrocytes swell and break up as do the other projections (fig. 18), and the space outside the so-called glia membrane of the vessels is filled with large bodies.

The acute changes in protoplasmic and fibrous astrocytes are the same except that when breaking up or swelling occurs in fibrous astrocytes, the fibers disappear. Chronically changed astrocytes may show an acute breaking up, just as previously normal cells do, and fragmentation with or without swelling may occur (fig. 19).

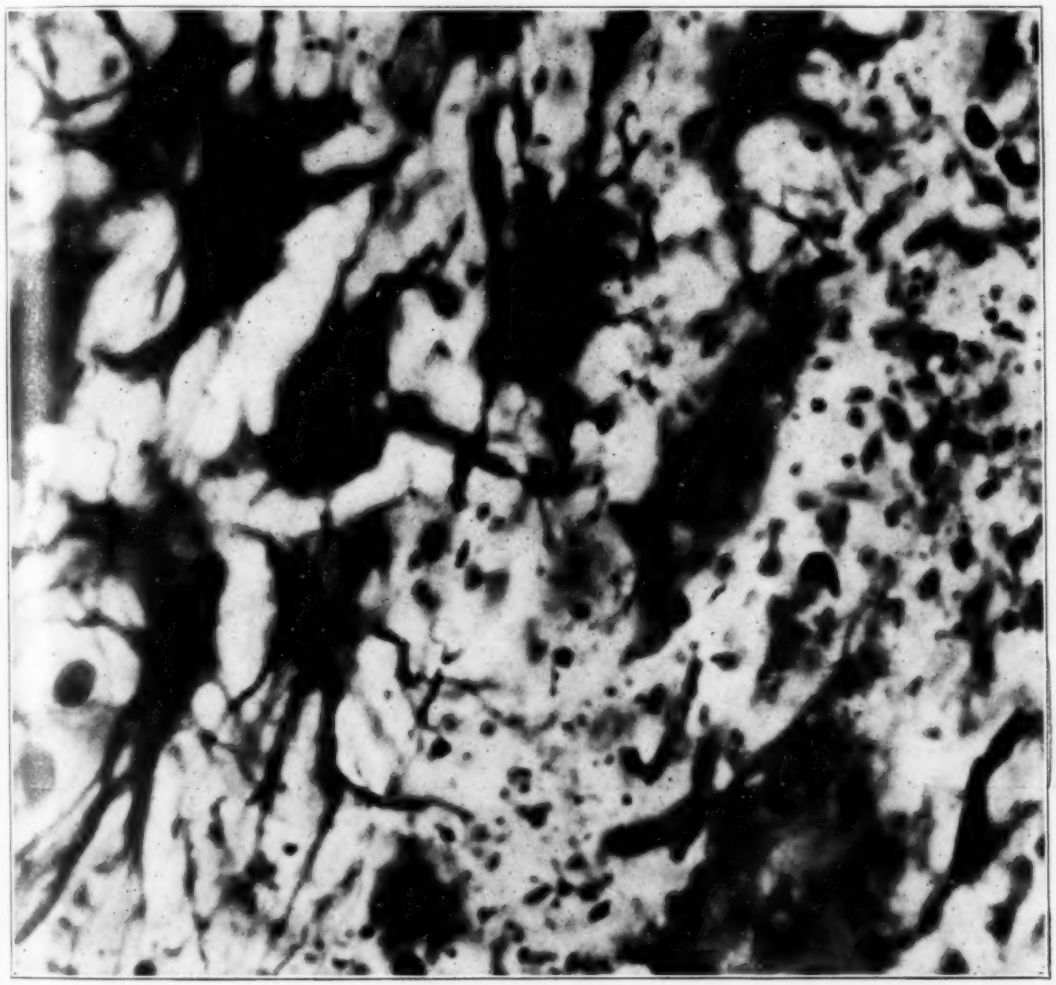

Fig. 19.—An acute change in chronically changed astrocytes. Fragmentation of the hypertrophied projections and swelling of the cells takes place just as it does in previously normal astrocytes. Hortega's silver carbonate astrocyte stain.

The acute change in astrocytes is different from the chronic change. They are compared in figure 20. The cell showing hypertrophy (fig. 20, *B*) is a protoplasmic astrocyte in the gray matter near a heavily encapsulated chronic abscess of the brain. The swollen cell with pyknotic

nucleus and fragmented projections is an ameboid form from the white matter adjacent to an unencapsulated acute brain abscess (fig. 20, *A*).

The forms which acutely changing astrocytes assume do not resemble developmental astrocyte forms. They are not phagocytic. They do not seem to have any function. The change is regressive and can easily be differentiated from the progressively changing astrocytes which may have an ameboid form. About the progressively reacting cell there are no fragmented expansions. The nuclei of such cells are not pyknotic. Multinucleated cells are seen, and amitotic division of nuclei is encoun-

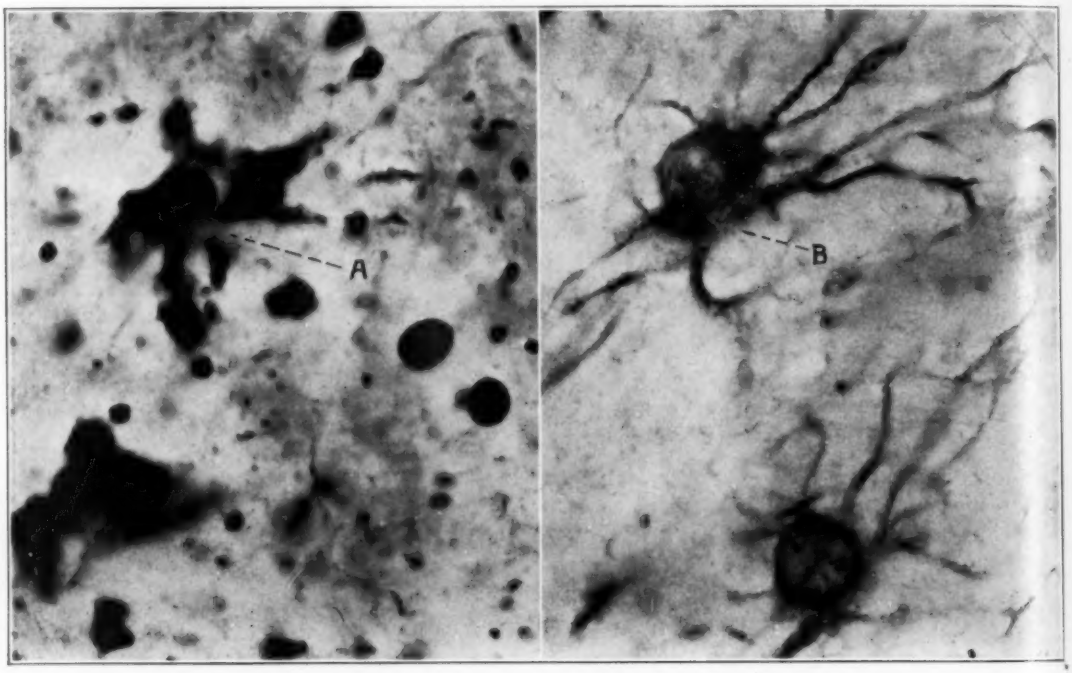

Fig. 20.—Comparison of the acute and chronic changes: *A* indicates ameboid glia in the wall of an unencapsulated recent brain abscess; *B*, hypertrophied astrocytes just outside the heavy connective tissue capsule of an old abscess of the brain. The nucleus in the ameboid or degenerating cell is pyknotic; that in the progressively reacting cell is large and stains lightly.

tered. Reacting cells of this type are well seen about wounds in the brain.

The exquisite vulnerability of neuroglia astrocytes in the acute diseases of the central nervous system was described by Eisath [10] and later by Alzheimer.[7] Eisath described an acute alteration in astrocytes in which the nuclei became pyknotic, the cytoplasm stained homoge-

10. Eisath, G.: Ueber normale und pathologische Histologie der menschlichen Neuroglia, Monatschr. f. Psychiat. u. Neurol. **20**:1, 139 and 240, 1906.

neously and the projections were swollen. Alzheimer elaborated Eisath's work and with new staining methods demonstrated that Eisath's ameboid forms contained characteristic staining granules. These granules were of two chief types: (*a*) methyl blue granules, and (*b*) fuchsinophil granules. The methyl blue granules were present as a result of the most

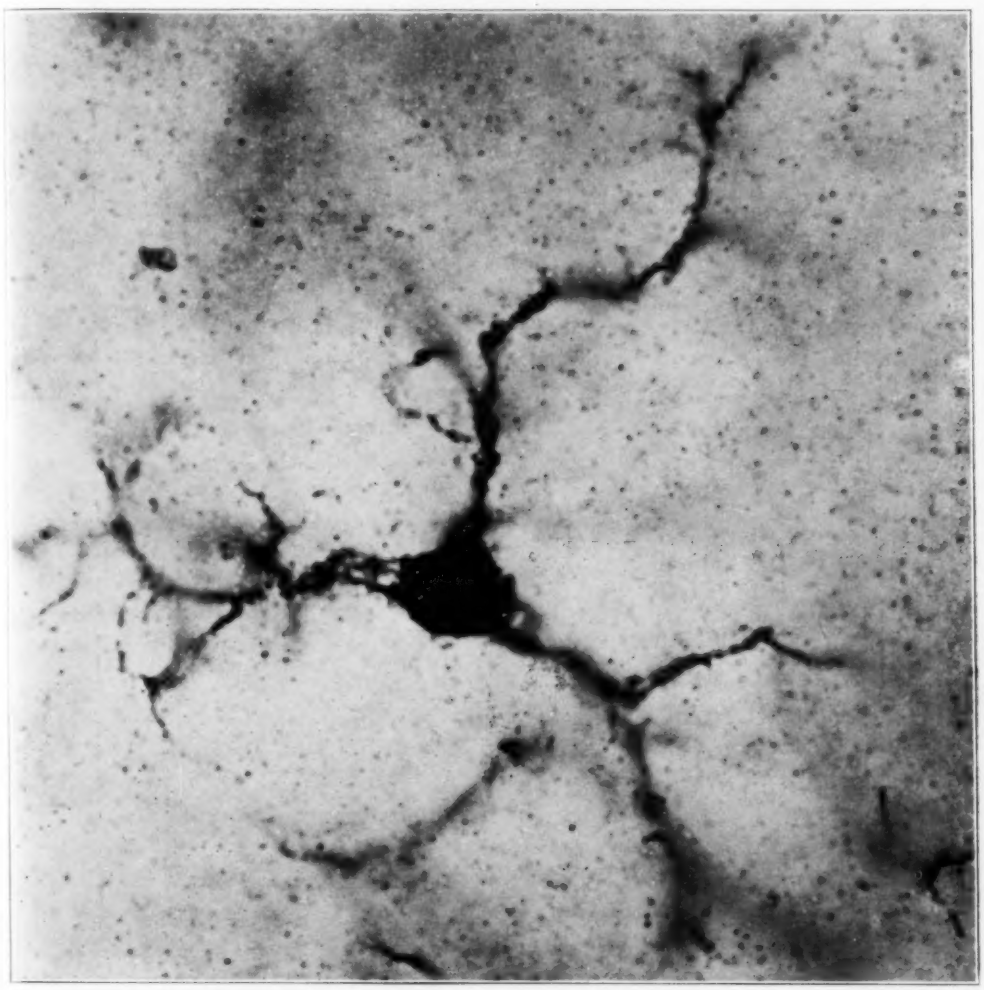

Fig. 21.—Normal microglia. The nucleus impregnantes deeply; little spines can be seen extending at right angles to some of the projections of the cell which are in this focus. Silver carbonate stain for microglia.

acute change. Large fuchsinophil granules were found when the change was somewhat more gradual. Alzheimer suggested that because large fuchsinophil granules were present at the same time in nerve cells that the ameboid forms were acting to transport waste or metabolic products

from nerve cells to vessels. By this he did not mean necessarily that the ameboid cells moved, but suggested that they might pass the products through their cell bodies to the vessels by way of the vascular attachments of the glia cells.

Fig. 22.—Changing microglia. The nucleus enlarges and the individual chromatin granules stand out; the cell body swells. Silver carbonate stain for microglia.

The conditions in which the acute changes in neuroglia occur with the formation of ameboid glia have been described by Eisath, Alzheimer, Rosental and Wohlwill.[11] In general, they are the acute diseases of the

11. Wohlwill, F.: Ueber amöboide Glia, Virchows Arch. f. path. Anat. **216**: 468, 1914.

central nervous system or chronic conditions in which acute upsets have occurred. They are listed by Alzheimer [7] as follows: infectious delirium; delirium; acute dementia praecox; status epilepticus; general paralysis of the insane; senile dementia; cerebral syphilis; progressive

Fig. 23.—*A* indicates changing microglia. The nucleus is vesicular; the cytoplasm increases and the cell body is irregular in outline but without the complicated projections present normally. Silver carbonate stain for microglia.

chorea; acute or subacute experimental intoxication; in the vicinity of tumors occurring in the margins of fresh softenings or abscesses; tuberous sclerosis; severe uremia; coma diabeticum; sepsis; cases in which the patients were unconscious for days before death.

Wohlwill,[11] after analyzing a large series of cases in which ameboid glia cells were found, concluded that they were best seen in conditions

accompanied by edema of the brain. He believed that the ameboid change was degenerative, occurring both during life and after death.

The development of specific staining methods has shown the validity of many of the conclusions drawn by these authors. That ameboid glia is a degenerative form of neuroglia has been clearly substantiated.

Penfield and Cone [12] studied the ameboid change, using both the staining methods of Alzheimer and those of the Spanish school. They emphasized that it was a degenerative process, evidence of oncoming cell death. They pointed out that it sometimes occurred during life in localized areas and that it also occurred diffusely throughout the central nervous system as an agonal or postmortem change.

The most acute alteration in astrocytes (fig. 11) found by them, as demonstrated by the metallic stains, was the type of cell in which by the metallic stains found by them, was the type of cell in which Alzheimer described the methyl blue granules. These authors found the fuchsinophil granules of Alzheimer in cells showing marked swelling (fig. 17). The fragmentation of the projections formed the filling bodies of Alzheimer. They pointed out that the clasmatodendrosis of Cajal,[13] the ameboid glia of Rio Hortega [14] and the ameboid glia of Alzheimer were the same change in astrocytes. As Hortega clearly pointed out, this acute change in astrocytes does not seem to have any function. It is a degenerating form and does not resemble an embryonic or developmental stage.

ACUTE CHANGES IN MICROGLIA

ROD CELLS AND COMPOUND GRANULAR CORPUSCLES

The acute changes in microglia differ markedly, both histologically and physiologically, from the acute changes in neuroglia. The normal microglia cell presents many delicate, complexly branching expansions from which short spines project at right angles. There is a small amount of cytoplasm about the elongated, densely unimpregnating nucleus (fig. 21). It is as if the cell were a resting cell.

The first transformation which microglia undergoes is indicated by hypertrophy of the cell body and an increase in the size of the nucleus. As the nucleus enlarges, the individual chromatin bodies in it become visible (fig. 22); the complicated projections become less ramified (fig. 23); the nucleus continues to enlarge, assumes a vesicular form and contains a few irregularly placed chromatin granules. Often at

12. Penfield, W., and Cone, W.: The Acute Regressive Changes of Neuroglia (Ameboid Glia and Acute Swelling of Oligodendroglia), J. f. Psychol. u. Neurol. **34**:204, 1926.

13. Cajal, S. R.: Contribucion al concemiento de la neuroglia del cerebro humano, Trab. d. lab. de invest. biol. **2**:255, 1913.

14. Del Rio-Hortega, P.: Sobre la verdadera significacion de las celulas neuroglicas llamada ameboides, Bol. de la Soc. españ. de biol. **8**:229, 1918-1919.

this stage the cell body is elongated, and typical rod cells are formed (fig. 24). This is especially notable when the cells undergoing this transition are present between rows of medullary sheaths in the white matter. As the transition progresses, the cytoplasm becomes laden with detritus and rounded (fig. 25). At this stage the nucleus is

Fig. 24.—Microglia rod cells. Here, microglia cells in transition are seen in rows between medullary sheaths; the nuclei are vesicular and the cell bodies are elongated. Silver carbonate stain for microglia.

small, irregular, pyknotic and laterally placed, and typical compound granular corpuscles have been formed. Among groups of cells showing the foregoing transitional stages occasional cells showing mitotic figures are present (fig. 26).

When del Rio-Hortega's silver carbonate method [2] for microglia is used, microglia and the transitional cells formed from it are selectively impregnated. When good results are obtained, either no other cell type is visible or only shadowy outlines of nerve cells and neuroglia are visible. Therefore, the transitions which microglia undergoes are clearly shown. Also after a selective impregnation has been obtained with silver, fat or iron stains can be carried out, and the increasing

Fig. 25.—Microglia phagocytes. Typical compound granular corpuscles filled with fat; the nucleus now is usually displaced to the side by the ingested material and it is pyknotic. Silver carbonate stain for microglia.

débris in the cell as it approaches the typical compound granular corpuscles can be followed.

In areas of degeneration where microglia is becoming actively phagocytic, groups of cells staining specifically with the silver carbonate method are seen on the outer part of the vessel walls. These cells have vesicular nuclei like reacting microglia. Occasionally they are so numerous as to form complete rings several layers deep about the vessel.

Sometimes mitotic figures are found (fig. 27). The cells at the outer margins of such groups show beginning elongation of their cell bodies as if being molded between the interstices of adjacent nerve tissue. This elongation of course, is present only when the degeneration or toxic process has not too greatly modified the architecture.

Fig. 26.—Microglia cell in mitosis. Silver carbonate stain for microglia.

Phagocytes in the instances just mentioned were formed from adult microglia in the gray and white matter and increased in number through mitotic division. Also, phagocytes with identical histologic and specific impregnation characteristics arose either from the walls of vessels or from cells in the perivascular spaces, and they, too, increased in number by mitotic division and entered the nervous tissue, not respecting the pial glia membrane.

The photographs of microglia shown have been taken from sections prepared in the study of routine autopsy material from human beings, and are from cases of anterior poliomyelitis and epidemic cerebrospinal meningitis. In the latter cases, ventricular puncture had been done and there was an opportunity to study the microglia reaction about

Fig. 27.—Mitotic figure in a cell in the adventitia or perivascular space of a vessel. The cell is impregnated with Rio-Hortega's silver carbonate method for microglia. It impregnates as selectively as microglia does and resembles transitional microglia seen out in the nervous tissue.

the brain needle track, ten days old at the time of death, as well as the reaction in the rest of the nervous system. It was the study of this last type of case particularly that emphasized the fact that neuroglia reacted as nerve cells do in acute diseases, that is, by degenerative

changes, but that in such conditions the microglia reaction is an active and not a regressive change.

The quick formation of phagocytes in destructive lesions of the central nervous system has been especially notable. True macrophages

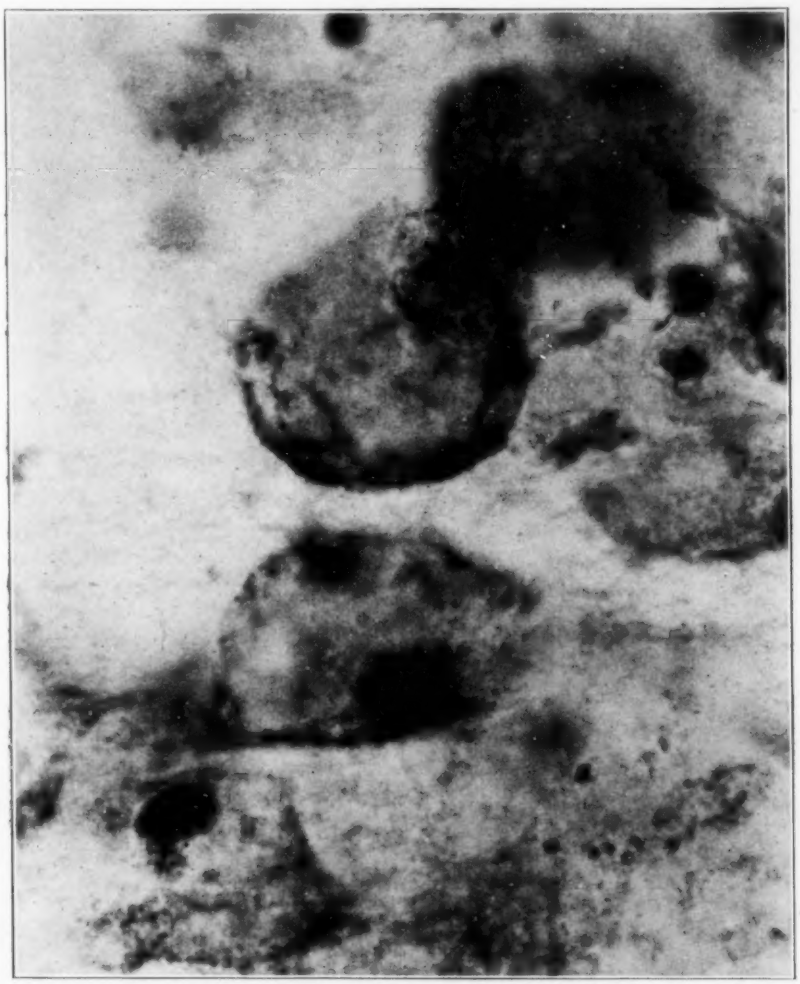

Fig. 28.—Phagocytes in a degenerating area of fibrosarcoma, selectively impregnated with Rio-Hortega's silver carbonate for microglia and resembling compound granular corpuscles.

were described by Farrar [15] as early as eighteen hours after experimental injury of the brain.

15. Farrar, C. B.: On the Phenomena of Repair in the Cerebral Cortex: A Study of Mesodermal and Ectodermal Activities Following the Introduction of a Foreign Body, Histol. u. histopath. Arb. ü. die Grosshirnrinde, Jena **2**:1, 1908.

The source of these phagocytes has been the subject of much discussion. Though they resemble macrophages in pathologic reactions in the rest of the body they have usually been considered to have a double origin in the brain. Alzheimer,[16] Merzbacher[17] and Lhermitte and

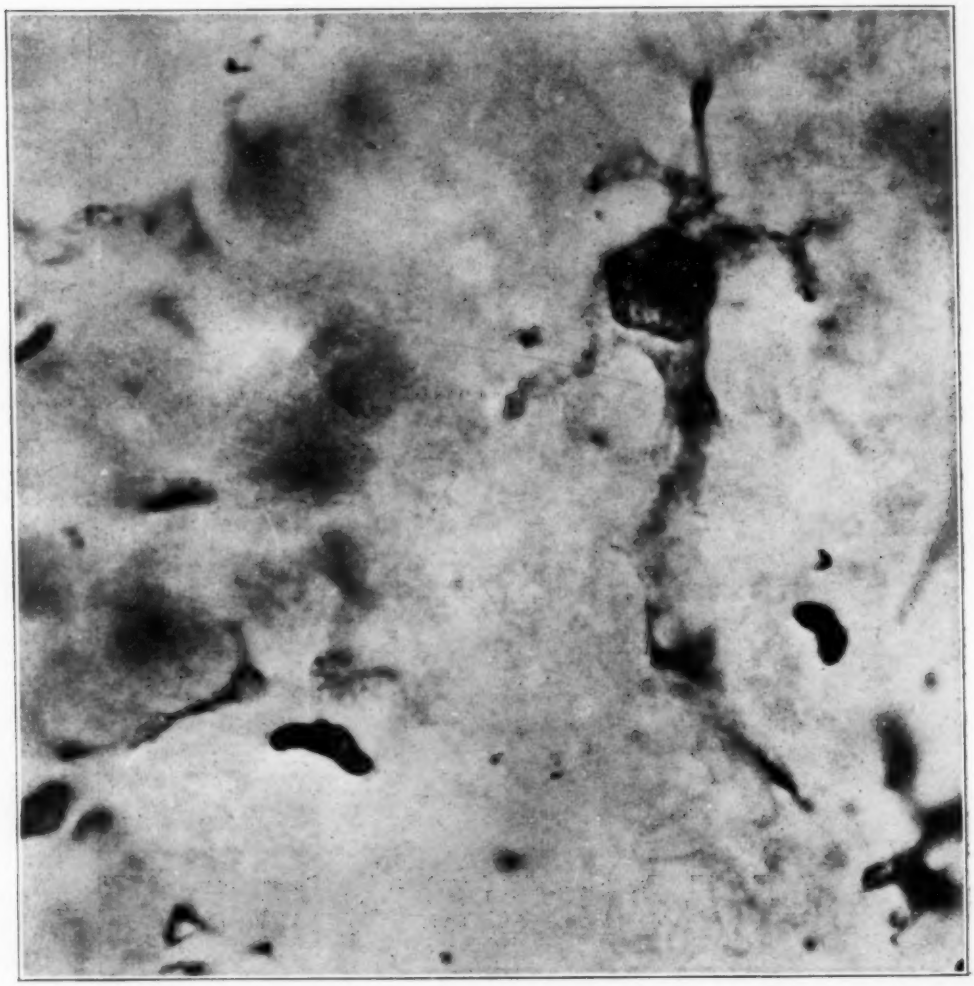

Fig. 29.—Phagocytes in degenerating area of a hypernephroma impregnated with the specific method for microglia. The resemblance to transitional microglia in the brain is close.

16. Alzheimer, A.: Histologische Studien zur Differenzialdiagnose der progressiven Paralyse, Histol. u. histopath. Arb. ü. die Grosshirnrinde, Jena **1**:18, 1904.

17. Merzbacher, L.: Untersuchungen über die Morphologie und Biologie der Abraumzellen im Zentralnervensystem, Histol. u. histopath. Arb. ü. die Grosshirnrinde, Jena **3**:1, 1910.

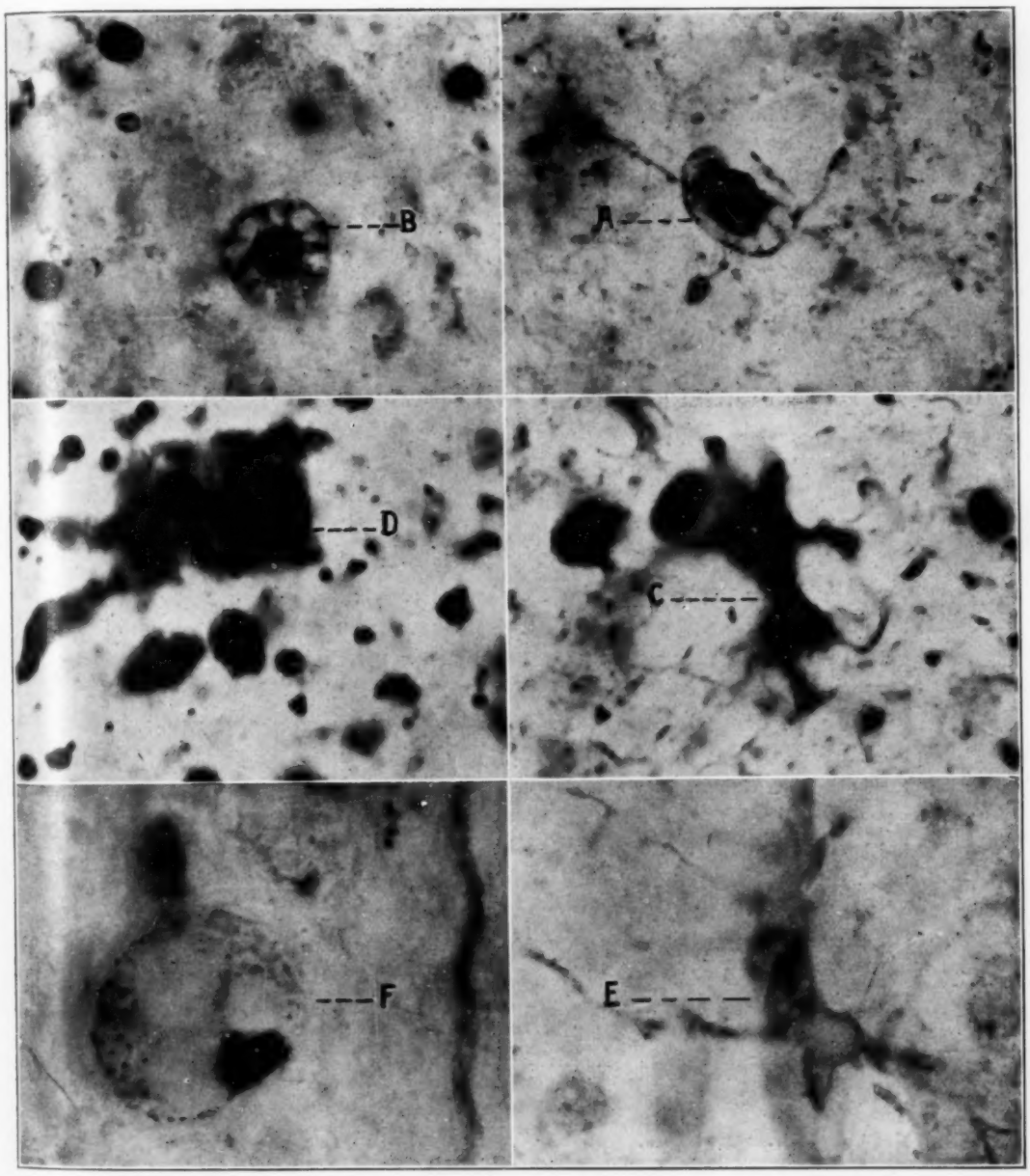

Fig. 30.—Comparison of the various stages of the acute changes in the interstitial cell groups: *A* and *B*, two stages in acute swelling of oligodendroglia; *C* and *D*, two stages in the ameboid change of astrocytes; *E* and *F*, two stages in the transition which microglia undergoes as it becomes phagocytic.

Schaeffer,[18] for example, believed that they arose from both mesodermal elements and neuroglia. In his article on general paralysis, Alzheimer pictures beautifully the origin of rod cells from vessels.

Del Rio-Hortega's brilliant work [2] has produced evidence to clear the controversy. He has pointed out the probable mesodermal origin of microglia, described its histologic and physiologic difference from neuroglia and insisted that it is from mesodermal elements alone that phagocytes in the central nervous system develop. With Asua,[19] Rio-Hortega showed that macrophages in the rest of the body and in tumors could be impregnated specifically with silver carbonate. In degenerating areas of tumors, cells resembling microglia in the brain with all its transitions, could be shown. These observations strengthened Rio-Hortega's belief that microglia was of mesodermal origin.

Penfield,[20] too, pointed out the similarity of phagocytes in muscle placed experimentally over wounds in the brain to those in the brain. All his observations point to the mesodermal nature of microglia. In figures 28 and 29, phagocytes in a fibrosarcoma and a hypernephroma have been impregnated selectively by Rio-Hortega's silver carbonate method, and their resemblance to reacting microglia in the brain is evident.

COMMENT

In addition to the foregoing studies I have examined the changes in the interstitial cells of the central nervous system in experimental cerebral embolism, in experimental wounds in the brain, in experimental acute intoxications and as they occur post mortem.

In experimental cerebral embolism, both nerve cells and neuroglia quickly break up at the center of the infarcted area. Their place is taken by great numbers of phagocytes. These phagocytes arise near vessels, and transitional microglia forms can be seen apparently approaching from the normal brain and increasing in number as they near the degenerated area. Similar pictures are seen early in wounds of the brain. Neuroglia's first reaction is degenerative, and it is only later that a progressive reaction on the part of neuroglia occurs.

In acute experimental intoxications, in which both astrocytes and oligodendroglia show acute degenerative changes alone, I have not

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18. Lhermitte and Schaeffer, H.: Les phénomènes reactionnels du ramollissement cérébral aseptique, leurs caractères differentiels avec l'encéphalite compliquée de ramollissement, Semaine méd. **30**:25, 1910.

19. Del Rio-Hortega, P., and de Asua, F. J.: Sobre la fagocytosis en los tumores y en otros procesos pathologicos, Arch. de cardiol. y hematol. **2**:161, 1921.

20. Penfield, W.: Phagocytic Activity of Microglia in the Central Nervous System, Proc. New York Path. Soc. **25**:71, 1925; Microglia and the Process of Phagocytosis in Gliomas, Am. J. Path. **1**:77, 1925.

encountered changes in microglia. Neither has microglia changed after death as does neuroglia.

This emphasizes the fact that the function of microglia differs from that of neuroglia. Microglia is the central nervous system's phagocyte. Neuroglia reacts in the acute diseases of the central nervous system by showing degenerative phenomena, and its marked vulnerability in these conditions suggests that its physiologic function is much more than that of a supporting tissue. If the acute disease of the central nervous system has persisted for a sufficient time to produce destruction of nervous tissue, then microglia reacts. Collado [21] described general changes in microglia in rabies, and Cone [22] recorded early alterations in microglia throughout the central nervous system in anterior poliomyelitis consisting of swelling of the cell body and a nuclear change suggesting beginning activity.

The most striking disagreement with Rio-Hortega's theory of the mesodermal origin of microglia comes from Metz and Spatz.[23] They agree that microglia constitutes a special cell group and that its function is phagocytic. They point out that it, together with the phagocytic cells in the adventitia of vessels, contains the iron pigment present in the brain in general paralysis. They, however, hold that its origin is ectodermal, and believe that it does not migrate.

CONCLUSIONS

1. There is a marked histologic difference in the acute reactions which neuroglia and microglia undergo (fig. 30).

2. Astrocytes and oligodendroglia react in acute disease of the central nervous system by degenerating as nerve cells do. Their change does not seem to have any obvious purpose, and it does not resemble an embryonic or developmental stage in the history of the cells.

3. Microglia responds in acute destructive lesions of the central nervous system to form rod cells and then compound granular corpuscles. It is not primarily affected by toxins or diseases which cause the acute degenerative changes in nerve cells or neuroglia. It reacts secondarily, changing not with, but after, degenerative lesions in nerve cells and neuroglia.

4. Microglia repeats its early developmental stages when it reacts.

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21. Collado, C.: Participacion de la microglia en el substratum patologico de la rabia, Bol. d. la Soc. españ. de biol. **9**:175, 1919.

22. Cone, W.: A Case of Anterior Poliomyelitis as Studied by the Newer Staining Methods, Proc. New York Path. Soc. **25**:78, 1925.

23. Metz, A., and Spatz, H.: Die Hortegaschen Zellen und über ihre funktionelle Bedeutung, Ztschr. f. d. ges. Neurol. u. Psychiat. **89**:138, 1924.

5. Metamorphosis from one cell group to another does not occur in the acute changes.

6. Astrocytes and oligodendroglia change quickly after death. Microglia resists postmortem alterations.

7. The study of the acute reactions supports the classification of the interstitial cells which Penfield [24] has advanced, i. e., neuroglia and microglia.

ABSTRACT OF DISCUSSION OF PAPERS BY DRS. PENFIELD AND BUCKLEY, GLOBUS AND CONE

Dr. George B. Hassin, Chicago: Is typical microglia encountered in the spinal cord? Most likely there is some, but I have never seen a typical microglia in the spinal cord such as is encountered in the brain. If the microglia in the spinal cord is so inconspicuous, how, in degenerative conditions of the spinal cord, could reactive phenomena be so markedly displayed by cells that are rare and probably do not exist? I mean to say that in degenerations of the central nervous system, the reactive phenomena that obtain are displayed by the neuroglia and not by the microglia of Hortega.

How old was the material of Dr. Globus? He showed excellent microglia cells which can be obtained only from fresh material.

Why did the speakers demonstrate their results only with the Spanish methods? Dr. Bailey was the only one who showed in contrast the changes in tumor cells stained with hematoxylin-eosin.

Dr. Hassin then demonstrated a number of slides stained by the older methods.

I could not obtain such pictures with the stains of Cajal. Pathologic studies should not be carried out with one stain exclusively. I was rather surprised that new staining methods had been used when the older stains are much more convenient, give better results and, in addition, can be used on old material, while the methods of Cajal have to be used on fresh specimens.

Aside from the fact that these methods bring out the changes clearly and in many instances even much more clearly than the Spanish methods, they also show that the reactive phenomena ascribed by the Spanish school to microglia are actually displayed by the neuroglia.

At least, in degenerations of the spinal cord the reactive phenomena in the form of formation of cytoplasmic glia, myeloclasts, myelophages, various types of gitter cells, adventitial vessel changes and other phenomena, as originating in the glia, can be splendidly followed up with the classic methods. Though I always use the Spanish methods, I find the older methods more convenient, not only because they give much better information and orientation as to the pathologic changes, but mainly because the results are not affected by the age of the material studied, which is not the case with some of the Spanish methods.

Dr. Armando Ferraro, New York: The main question is whether the microglia participates only in the formation of "gitter cells" or whether there are also other types of glia cells; the astrocytes, which enter into the formation of the gitter cells. All the speakers have shown the transformation of microglia into gitter cells, but have failed to prove that astrocytes do not participate in the formation of these cells. I do not deny that the microglia participates in their formation, but I would like to have special studies proving that astrocytes do not. As a matter of fact, transitory forms between the fixed type of

24. Penfield, W.: Neuroglia and Microglia, in Cowdry: Special Cytology, New York, Paul B. Hoeber, to be published.

abbau cells and gitter cells can be found in many diseases. In Sachs' amaurotic idiocy transitory forms may be found, and in encephalitis periaxialis diffusa I have also been able to follow, by the use of special stains, the transitory phases from astrocytes into gitter cells. If the morphologic conception of del Rio Hortega is adopted, one must also admit that the astrocytes participate also in the formation of the gitter cells.

There is another point. Dr. Cone has shown some acute degenerative changes of the astrocytes. Some of these pictures are suggestive of the transformation of astrocytes into gitter cells. I would like to know if Dr. Cone has proceeded with special methods (special methods for fat stain) to find out the end-result of this acute type of degeneration.

Finally, there is the problem of the oligodendroglia. What material is found around these cells in the so-called acute swelling of the oligodendroglia? Is it fat material? If that can be established, as well as their transformation in abbau cells, then the proof may be produced that ectodermic elements as well as mesodermic elements will both participate in the formation of the gitter cells.

Dr. Walter Freeman, Washington: I should like to ask Dr. Penfield whether the external granular layer that is found in the cerebellum constitutes the source of the microglia cells? I am not acquainted with the nature of these cells.

I should like to ask Dr. Buckley about the response of the microglia to these brain punctures? He has dealt with the connective tissue response rather than the gliosis, but if the connective tissue does enter into it and if Dr. Penfield's thesis that the microglia is of mesodermic origin is valid, surely a study of these cells would be of great importance.

Along that line, I should like to ask Dr. Globus whether the soft lining membrane, which he said was not glia but was necrotic material, was studied for connective tissue, because in artificial cerebral injuries connective tissue repair is one of the most important things. If there is regeneration of the connective tissue in response to artificial injuries to brain tissue, may it not also take place in response to natural injuries? Is there any evidence that this internal so-called necrotic membrane is connective tissue?

It seems to me that we ought to endeavor to explain these morphologic changes which are recognized in the glia on physicochemical states and try to hitch them up with similar processes seen elsewhere in the body. The central nervous system offers an excellent location for studying these changes because the cells are so isolated and it is a real pleasure to look over preparations in which each cell is silhouetted, but when we talk to pathologists who are not well acquainted with changes in the nervous system and speak of acute swelling of the oligodendroglia, and conditions like that, they look askance at us. If we could confine ourselves to speaking of hydropic degeneration, wouldn't it make our language more compatible with theirs?

Dr. Wilder Penfield: It seems to me that the different point of view which each of the spreakers has presented, that is, Dr. Globus, Dr. Cone and Dr. Bailey, has provided a certain amount of evidence, direct or indirect, that the phagocytic cells of the brain are of a different order from the ectodermal neuroglia, and that microglia likewise is of a different order. Dr. Globus showed us the transitions from microglia to the compound granular corpuscle. Dr. Ferraro also has agreed that there is such a transition, and Metz and Spatz have agreed to such a transition in their work in Germany.

Dr. Cone showed that in the acute changes of the astrocyte and oligodendroglia there is no evidence, by the stains that are used, of transformation into compound granular corpuscles. There is evidence that there is a destructive process in the ectodermal cells.

Dr. Bailey, after covering the huge number of tumors that he has studied, does not find microgliomas. If the microglia is an ectodermal cell and is a

part of the glia, why do we not see such tumors? You can study transitions from a normal microglia at a distance to the compound granular corpuscles around the degenerating cells of either astrocytomas or spongioblastomas.

It is certainly true that it is impossible to prove that the one cell develops from the other. In fact many sins of interpretation have been committed on the grounds of evident transition from one cell to another, but the classification which I have outlined in my paper affords a simplification, not an increased complexity, of the work, and does not contradict the work of Alzheimer, Nissl, Spiller and the rest of the men who have contributed so much, but adds a supplement to it. Nissl believed that the compound granular corpuscle was mesodermal. Alzheimer, in many of his communications, seems to be puzzled about the distinction between the fixed abbau cell and the mobile one.

In his study, Dr. Cone states that there is no evidence of a change in the compound granular corpuscles. In the work which I did with del Rio Hortega, which has not yet been published, we carefully studied a series of wounds in the brain; we studied the astrocyte change around the wounds, following it from day to day. With each day's change, there was destruction, hypertrophy and fibrillation of the astrocytes, but no evidence of transition from the astrocytes to the compound granular corpuscles. That is negative evidence. All our evidence must be negative. But it seems rather unreasonable to me to have a cell which does have a certain phagocytic function formed by two entirely different types of cells, an ectodermal and a mesodermal cell. Everywhere in the body it is the mesodermal cell that provides macrophages.

In regard to the microglia in the spinal cord: they can be stained there, but with somewhat more difficulty for some reason or other. If one stains them in the spinal cord of young animals, they first appear just beneath the pia. Later they can be stained mostly in the gray matter but also in the white matter of the cord.

I do not want to give the impression that we rely on the silver methods at the expense of the ordinary methods because we do not, but the silver methods help to explain and fill in gaps where the ordinary methods are vague. We use the phosphotungstic acid method of Mallory perhaps more than any other single method.

The external granular layer of the cerebellum is not, so far as I know, a source for microglia. The three areas where microglia is formed in largest numbers are the only three areas in the brain where pia is next to the white matter; that is, over the cerebellar peduncles and where the area of the pia is invaginated to form the tela choroidea superior and inferior. In these areas in which myelinization is in progress there may be some sort of stimulation which causes compound granular corpuscle to be formed from the undersurface of the pia.

Just a word about tumors of the nervous system. Dr. Bailey's paper, it seems to me, and the work that has been done recently in America on tumors of the brain, is of the utmost importance and is beginning to clear up the vagueness which we find in the literature particularly on gliomas. In going over the tumor material from the Neurological Institute we find that both as to biologic activity and as to histologic traits the tumors seem to fall easily into the classification that Dr. Bailey has given us. The spongioblastoma multiforma of Globus and Strauss (the bête noir of the neurological surgeon) regularly is malignant. The patient is not influenced by any treatment. The medulloblastoma of Cushing and Bailey also we feel is a perfectly definite entity. It is influenced by roentgen-ray treatment, as Dr. Bailey pointed out. The astrocytoma, from which patients are apt to recover at least temporarily, is recognized as a definite entity. The ependymoma likewise is an easily recognized entity. The other rarer tumors, particularly the oligodendroglioma, the spongioblastoma unipolare and the astroblastoma may or may not prove to be biologic entities. But whether they are named rightly or not is of little importance. That they form groups and that they are all benign and that the patients survive for a long period is of the utmost importance.

DR. R. C. BUCKLEY: In answer to Dr. Freeman, a transformation of the microglia into the compound granular corpuscles was seen in a number of sections about the blunt-needle tracts.

DR. JOSEPH H. GLOBUS: In answer to Dr. Hassin, recently in the study of a case of acute multiple sclerosis, an unusual pathologic specimen, I was able to demonstrate conclusively the presence of microglia, and, among them, cells which can be regarded as the forerunners of gitter cells (compound granular cells).

My material is as fresh as can be obtained, usually within twelve to twenty-four hours after death, and is fixed in formaldehyde.

It is interesting that Dr. Hassin and Dr. Ferraro both base their conclusions on results with the older glial methods. It is because Dr. Hassin relied entirely on old methods that he failed to see microglia in amaurotic family idiocy. In my studies of amaurotic family idiocy, I found a certain cell form which, for the lack of precise knowledge, I called "mulberry" cells. They show numerous little processes which envelop small vacuoles. It is this cell form which was erroneously regarded as an artifact. Such cells when studied with the newer method may be recognized as microglia which has undergone changes and had assumed the character of the so-called giant microglia of Cajal.

Of course, other staining processes were used besides the silver carbonate methods, including also Herxheimer's scarlet red process.

I have studied astrocytes with an open mind. I was unable under any circumstances, by the old as well as by the modern method, to trace the astrocytes into the formation of compound granular cells.

In the early stages you do see the membrane. Membranes have been described for all cysts (fibrous connective tissue membranes), but they are likely to undergo degeneration with a structureless zone as the result. The fibrous connective tissue is not maintained long.

As to the double origin of the gitter cells, that is well known. They may, as we have recently shown in acute epidemic encephalitis, arise from lymphocytes and, as was demonstrated here, take origin from changed Hortega cells.

I would like to say a word about Dr. Bailey's presentation. I was happy to see that he had taken the medulloblastoma away from the group of spongioblastoma and placed it where it belongs, among the less differentiated type of primary tumors of the brain, and has assigned to the spongioblastoma multiforme its deserving place. The fact that a type of cell which is astrocytic is occasionally found in a spongioblastoma or any other type of gliogenous tumor should not be disconcerting. There is always in any new growth a stray cell which will show a more differentiated form, but that is not the cell which determines the character of the tumor. The character of the tumor usually depends on the dominating cellular type. So, an occasional undifferentiated or specialized cell should not disturb one too badly.

DR. WILLIAM V. CONE: Dr. Globus presented before the society a year ago a procedure which makes old material available for the new methods of impregnation. Many of the sections which I showed in my presentation were sections which had been treated according to his method. Dr. Globus[25] advises placing frozen sections of old formaldehyde fixed material in ammonia water over night. They are then treated with hydrobromic acid. This introduces the ammonium-bromide which seems so necessary in the Cajal and Hortega metallic methods of impregnation. Beautiful sections of microglia and neuroglia can be obtained by using this modification.

Regarding Dr. Freeman's question as to the origin of compound granular corpuscles, this can be answered convincingly by the following experiment:

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25. Globus, J. H.: The Cajal and Hortega Glia Staining Methods: A New Step in the Preparation of Formaldehyde-Fixed Material, Arch. Neurol. & Psychiat. **18**:263 (Aug.) 1927.

If melted paraffin is injected into the common carotid artery of a dog, areas of infarction can be produced in the brain. In these infarcted areas, neuroglia and nerve cells degenerate, and this change is evident early. At the center of such an area neuroglia may entirely disappear. The early change in both nerve cells and neuroglia is purely degenerative. The change in microglia in such an area is different, and its transition to form compound granular corpuscles can be clearly traced if specific staining methods are used. Transitional forms of microglia are particularly well seen at the margin of the softened area. This change in microglia is a progressive one.

We have used Alzheimer's methods nos. 4, 5 and 6 and have found that they stain both neuroglia and microglia. Since these methods are not specific it is difficult to trace the transitions which the various cell groups undergo. When the specific metallic methods of impregnation are used and the technical results are good, one can say with considerable certainty that astrocytes do not form phagocytes and that phagocytes are formed from microglia.

Dr. Percival Bailey: I have made a classification of the gliomas, but classification is only the first step in a scientific investigation and should not be the last. Classifications are made to be abandoned intelligently. Some one has remarked recently in the Atlantic Monthly that we no longer look at the world through Aristotelian glasses and say that the whole world is composed of classes in which all members look alike. The world is made up of variants, among which certain family resemblances may be traced. The same is true of gliomas. No two gliomas look alike; still certain family resemblances may be seen, and it is these family resemblances which I have tried to trace. If an atlas is made of gliomas and one tries to compare any given tumor with its plates, the correspondence will not be exact. There is only a grouping of the gliomas and one should not expect to find any glioma looking like every other one in these classes.

As to "Gitterzellen" I think that they come from different sources. One is the microglia, without doubt, if one understands by "Gitterzellen" a phagocytic cell which picks up dead material and carts it off to the blood vessel or elsewhere; I do believe, however, that one can get a morphologic picture of an astrocyte which looks much like a "Gitterzell," and I think the confusion is due to the fact that fat is used as an index of phagocytic activity. Fat is a bad material to use as an index because there may be fat granules dotted around in an astrocyte from a purely degenerative change. One sees that often in degenerative processes. When the body of the astrocyte has fat granules scattered in it, it looks like a gitter cell.

I want to point out the fact that a blunt brain-puncture needle is used because if a sharp needle is used and the brain is punctured, blood vessels will be punctured and the patient will sometimes die owing to hemorrhage from an artery. But a blunt needle pushes the blood vessel to one side and the needle can be insinuated down into the tissue. I do not think a sharp needle should be used for that purpose.

In the oligodendroglia, when they swell, some pathologic substance is laid down, the chemical nature of which I do not know. I know it will stain slightly with scarlet red. As the cell swells up, something which gives the staining reaction of mucin is laid down in those cells. At the same time it gives the chemical reaction of lipoids. I do not know what its chemical nature is.

THE CEREBRAL CIRCULATION

IV. THE ACTION OF HYPERTONIC SOLUTIONS

PART I *

H. G. WOLFF, M.D.
AND
H. S. FORBES, M.D.
BOSTON

Intracranial pressure may be strikingly changed by varying the osmotic pressure of the blood. The intravenous or intraperitoneal injection of hypertonic dextrose, urea or sodium chloride [1] may lower the intracranial pressure from normal to levels well below atmospheric pressure.[2] In this paper we have studied the effects of such hypertonic solutions upon the diameter of the pial arteries and veins during the typical intracranial pressure response. In each of the six animals examined very definite constriction of these vessels occurred at the height of the response.

Many organs contribute in the transfer of fluids from the tissues into the blood after the injection of hypertonic solution, although some contribute more than others. It is known that the brain and cerebrospinal fluid are greatly reduced in volume.[3] Moreover, associated with shrinkage of the tissue, there may be alteration in function, especially in smooth muscle. Hughson and Scarff [4] have noted increase in intestinal tone and peristalsis after injection of hypertonic salt solution. Campbell [5] confirmed this and observed coincidently pallor of the gut which he attributed to vasoconstriction, perhaps resulting from the increased tonus of the gut. Similar increase in tone and peristalsis follows injection of hypertonic solutions of sodium citrate and sodium bicarbonate. Pilcher and Sollmann [6] noted vasoconstriction in the perfused spleen after intravenous injections of physiologic sodium chloride solution. They attributed this to stimulation of the vasomotor center.

The intravenous injection of hypertonic solutions of sodium chloride, dextrose or urea results in an elevation of systemic arterial blood

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* Read at the Fifty-Third Annual Meeting of the American Neurological Association, Atlantic City, N. J., May, 1927.

* From the Department of Neuropathology, Harvard Medical School.

1. Weed, L. H.: Am. J. Physiol. **48**:101, 1921.
2. Fremont-Smith, F., and Forbes, H. S.: Intra-Ocular and Intracranial Pressure, Arch. Neurol. & Psychiat. **18**:550 (Oct.) 1927.
3. Weed, L. H., and McKibben, P. S.: Am. J. Physiol. **48**:531, 1919.
4. Hughson, W., and Scarff, J. E.: Bull. Johns Hopkins Hosp. **35**:197, 1924.
5. Campbell, R.: Unpublished results, personal communication to the authors.
6. Pilcher, D., and Sollmann, T.: Am. J. Physiol. **35**:70, 1914.

pressure after a short period of fall. There is at the same time a slight rise and then a fall in systemic venous pressure and a slight fall in intracranial venous pressure.[7] The sagittal sinus and brachial venous pressures approach each other at a level somewhat lower than the control. After an initial rise there is a great decrease in cerebrospinal fluid pressure concomitant with shrinkage of the brain. Howe and McKinley,[8] however, could not observe any alteration in the diameter of pial blood vessels after the injection of 10 cc. of 25 per cent sodium chloride or 100 per cent dextrose. Wearn and Richards [9] observed the minute vessels of the kidney decrease in caliber after the injection of hypertonic saline solution even though the total urine secretion increased.

METHOD

The method employed has already been described in detail.[10] The pial blood vessels of anesthetized animals were observed by microscope through a glass window in the skull. The vessels were measured and photographed, and coincident measurements of cerebrospinal fluid and blood pressures were recorded. The animals (cats) were anesthetized with 1 per cent iso-amyl-ethyl barbituric acid.

Cerebrospinal fluid pressure was registered by a 1 mm. bore glass manometer, filled to a point 100 mm. above the cistern with Ringer's solution, and connected by a rubber tube and a needle with the cisterna magna. Systemic arterial pressure was measured by a mercury manometer, and a cannula in the femoral artery. In all the experiments, at one minute intervals or less, observations were made of the various pressures and of the diameter of the pial artery under observation. Graphic charts have been made from the data thus obtained.

The following solutions were injected intravenously and intraperitoneally: from 10 to 20 cc. of 30 per cent solution of sodium chloride; 20 cc. of 50 per cent solution of dextrose, and 10 cc. of 50 per cent solution of urea.

EXPERIMENTS

EXPERIMENT I.—*Action of Sodium Chloride (Injected Intravenously).*—A cat weighing 4.75 Kg. was used. It was anesthetized with 42.7 cc. of 1 per cent iso-amyl-ethyl barbituric acid, intraperitoneally. After a short control period, 10 cc. of a 30 per cent solution of sodium chloride was injected intravenously over a period of five minutes. The arterial pressure immediately fell 48 mm. of mercury and then within two minutes rose 70 mm. of mercury; again it fell 64 mm. of mercury before the sodium chloride was wholly injected. Following a slight initial constriction, the pial artery dilated 23 per cent; within two minutes it

7. Weed, L. H., and Hughson, W.: Am. J. Physiol. **58**:53, 1921; **58**:101, 1921.

8. Howe, H. S., and McKinley, E.: Cerebral Circulation, Arch. Neurol. & Psychiat. **18**:81 (July) 1927. The authors observed the vessels through an open trephine hole but made no measurements before or after the experimental procedures. It is quite possible that slow changes in diameter escaped detection.

9. Wearn, J. T., and Richards, A. N.: J. Biol. Chem. **66**:247, 1925; also personal communication to the authors.

10. Forbes, H. S.: The Cerebral Circulation, Arch. Neurol. & Psychiat. **19**:751 (May) 1928. Eli Lilly & Co., of Indianapolis furnished the material for experimental purposes.

had constricted to less than its original size and then, at the end of the period of injection, had again dilated. The changes in cerebrospinal fluid pressure paralleled those of the pial artery during the period of injection. When the injection was completed the cerebrospinal fluid pressure fell 90 mm. of Ringer's solution in fifteen minutes and remained more or less constant; the changes in diameter of the pial artery and vein were at first parallel. Fourteen minutes after the injection was completed, the artery constricted to 62 per cent of its original size. The artery gradually returned to normal, although the diameter of the vein and the intracranial pressure were still low.

EXPERIMENT II.—*Action of Dextrose (Injected Intravenously).*—A cat weighing 3 Kg. was used. It was anesthetized with 24 cc. of 1 per cent of iso-amyl-ethyl barbituric acid, intraperitoneally. After a control period of fifteen minutes, an intravenous injection of 20 cc. of a 50 per cent solution of dextrose was started. During the four and three-quarter minute period of injection the cerebrospinal fluid pressure rose, the arterial pressure fell, and the pial artery dilated. Following a brief rise, the cerebrospinal fluid pressure finally reached its maximum height when the arterial pressure was lowest, and during the dilatation of the pial artery. As the arterial pressure rose 72 mm. of mercury, the cerebrospinal fluid pressure fell, and the pial artery constricted 16.6 per cent. It then gradually returned to normal.

EXPERIMENT III.—*Action of Urea (Injected Intravenously).*—A cat weighing 3.85 Kg. was used. It was anesthetized with 30.8 cc. of 1 per cent iso-amyl-ethyl barbituric acid, intraperitoneally. After a control period of seven minutes, 12 cc. of 50 per cent urea was injected intravenously over a period of four minutes. The arterial pressure fell 57 mm. of mercury in three-fourths of a minute and then quickly rose. The pial artery dilated during the periods of the fall in blood pressure, and at the end of the period of injection the diameter was 20 per cent greater than originally. Following dilatation, the artery constricted rapidly at first and then gradually until it was 87.5 per cent of its initial diameter. The arterial pressure continued to rise and the cerebrospinal fluid pressure to fall. The pial vein constricted with the artery, but remained constant after reaching a diameter 80 per cent of its original size. After this the artery gradually dilated and returned to normal, while the intracranial pressure remained low.

EXPERIMENT IV.—*Action of Sodium Chloride (Injected Intraperitoneally).*—A cat weighing 3 Kg. was used. It was anesthetized with 24 cc. of 1 per cent iso-amyl-ethyl barbituric acid, intraperitoneally. After a control period of fourteen and one-half minutes 20 cc. of 30 per cent solution of sodium chloride was injected into the peritoneal cavity. The arterial and cerebrospinal fluid pressures immediately rose, while the pial artery constricted. The vasoconstriction continued slowly; twenty-four minutes later it had constricted 10 per cent; one-half hour later, 26 per cent. Two minutes after the injection, the arterial and cerebrospinal fluid pressures reached their maximum height and then fell, the latter 267 mm. of Ringer's solution in forty minutes. The pial vein constricted at first parallel with the artery, but returned to its initial size while the artery was still constricting. At *x* (fig. 6), Ringer's solution was permitted to flow into the cistern until it reached a pressure of 100 mm. of Ringer's solution. The pial artery constriction still continued.

OBSERVATIONS

When the solutions were rapidly injected intravenously there was an initial dilatation of the pial arteries and arterioles, accompanied by a

fall in systemic arterial pressure.[11] During the fall in systemic arterial pressure the cerebrospinal fluid pressure ascended. However, if the intravenous injections were made slowly or by the intraperitoneal route, no vasodilatation or fall in blood pressure was noted. After the first stage, there occurred a gradual fall in cerebrospinal fluid pressure and a slow decrease in the size of the pial arteries, arterioles, minute vessels and veins. This was followed by a gradual rise in systemic arterial blood pressure. Elevation in blood pressure was more striking and of longer duration if the injection was made intravenously. If the injection

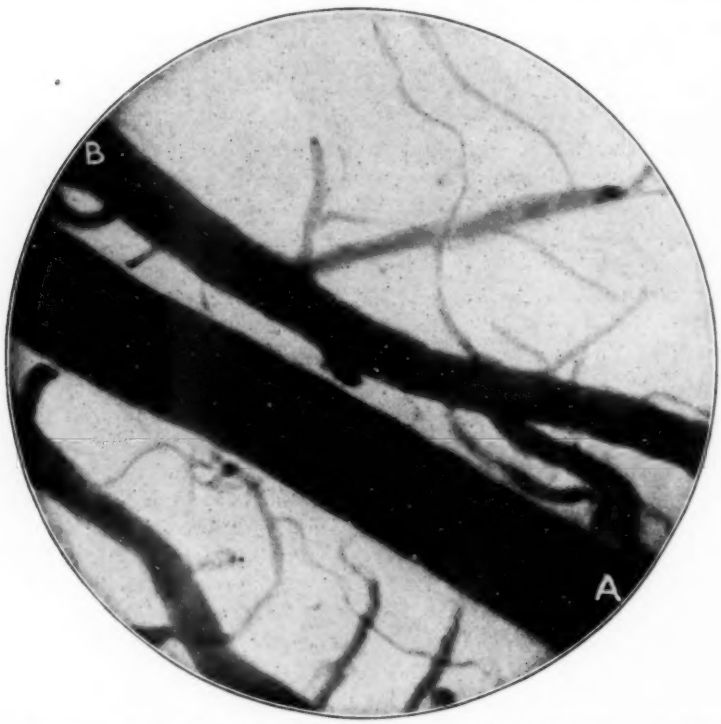

Fig. 1 (experiment IV).—Pial blood vessels before injection of hypertonic sodium chloride intraperitoneally. Actual magnification of photomicrograph is × 68. In this and in figure 2, *A* indicates arteryl; B, vein.

was made intraperitoneally, after a brief rise there might be a slow fall. After the peak of pial vasoconstriction had been reached, the diameter gradually returned to normal. In all instances, the pial vessels returned to their original size before the intracranial pressure reached its initial level.

11. Brief periods of fall of arterial pressure even after the injection of 2 cc. of isotonic salt solution intravenously have been recorded by Reid Hunt (Am. J. Physiol. **45**:197, 1918). He concluded that one of the "vasodilator mechanisms" was involved.

To control the experiments in which hypertonic solutions were injected, 30 cc. of isotonic salt solution (NaCl) was injected intavenously. The pial artery in no instance changed in diameter.

COMMENT

The photographed and measured pial arteries, arterioles, veins, venules and minute vessels all constrict after intravenous or intraperitoneal hypertonic solution (figs. 1 and 2). The maximum constriction of these blood vessels and the greatest rise in systemic arterial

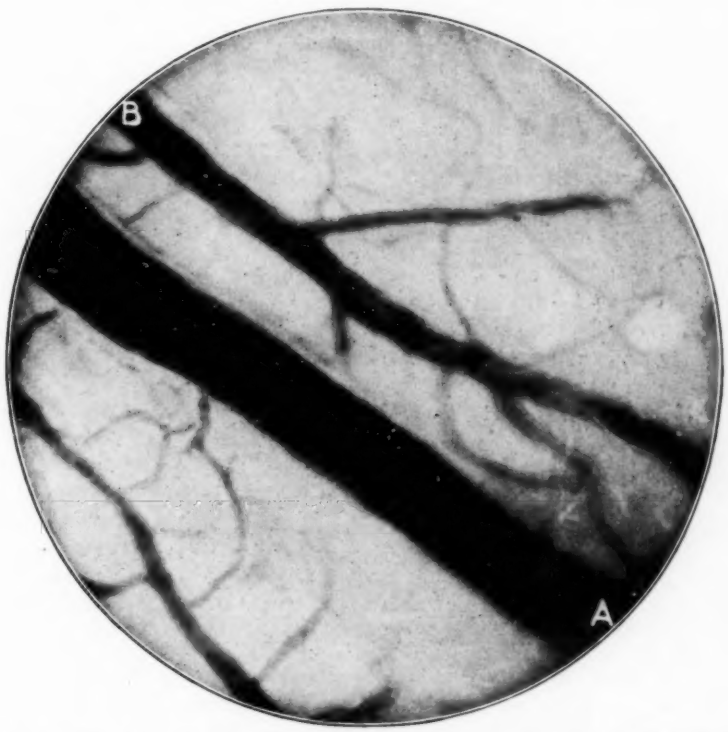

Fig. 2 (experiment IV).—Pial blood vessels fifteen minutes after the injection of hypertonic sodium chloride. Actual magnification of photomicrograph is × 68. Note the constriction of all visible vessels on the surface of the brain.

blood pressure after intravenous injection may occur coincidently (fig. 3). The vasoconstriction after hypertonic solution is clearly not collapse from decrease in intravascular pressure, since the arterial pressure is usually elevated during the pial vasoconstriction. Moreover, the extravascular pressure is greatly decreased, while the vasoconstriction continues. From consideration of these pressure relationships it must follow that the pial artery diameter is not dependent on either intravascular or extravascular pressure.

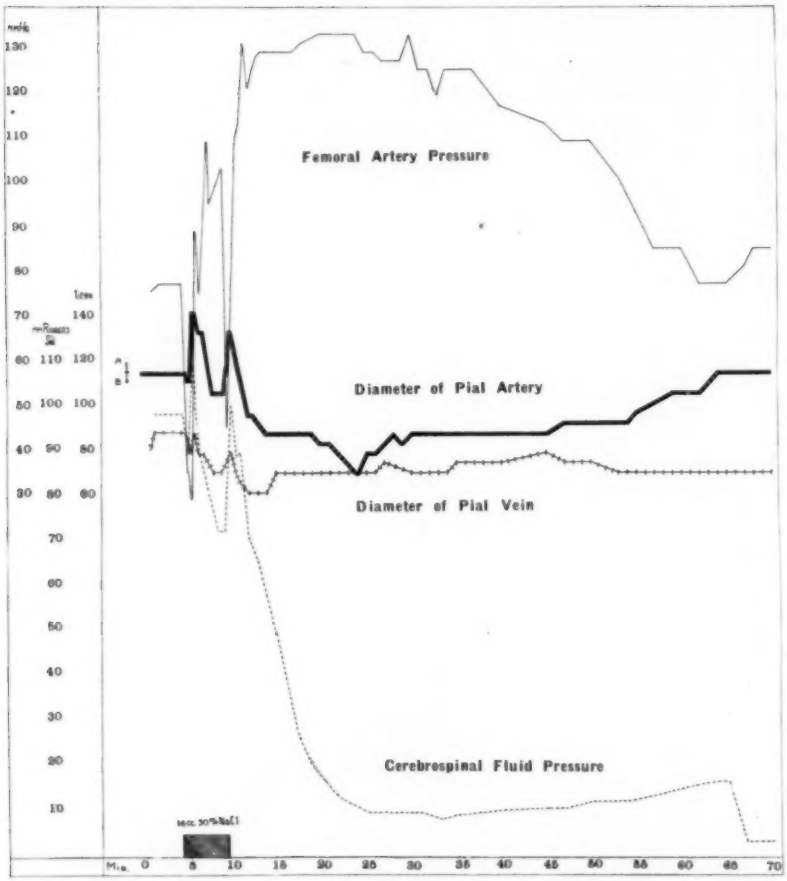

Fig. 3 (experiment I).—Action of sodium chloride administered intravenously. In this and the following charts ordinates represent millimeters of mercury, microns and millimeters of Ringer's solution, respectively. Abscissas represent time in minutes. Observations of systemic arterial and cerebrospinal fluid pressures and diameters of the pial artery were made at one minute intervals or less in all instances. The cross hatched areas or arrows at the bottom of charts indicate periods of injection. The broad line indicating the diameter of the pial artery is so plotted that its upper edge records the correct measurements and time relations. The narrow line represents the femoral artery pressure, and the broken line, the cerebrospinal fluid pressure and the crossed line the diameter of the pial vein. The arrow *AB* (9 microns) represents a change in arterial diameter which could be accurately measured. A change of half this extent is of doubtful validity.

The reactions here described cannot result from the injection of special ions, since the same reaction follows the introduction of several different substances.

Since the intravenous injection of 30 cc. of isotonic sodium chloride solution had no influence on the diameter of the pial artery, it may be concluded that increase of 30 cc. in blood volume and the act of intravenous injection were not in themselves responsible for the constriction of the pial artery.

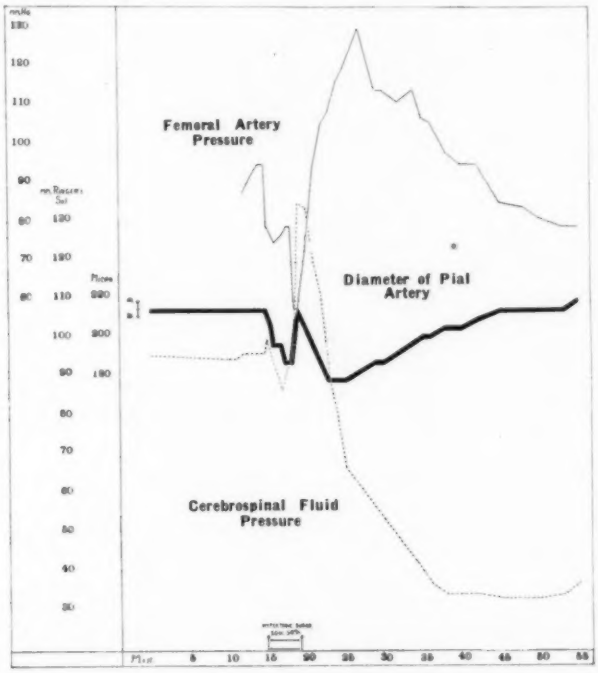

Fig. 4 (experiment II).—Action of dextrose administered intravenously.

The dilatation of the pial arteries with fall of systemic arterial pressure (figs. 3, 4 and 5), and the constriction with rise in arterial pressure, indicate that the pial arteries and the systemic vessels respond to the stimulus in a similar manner.

Shrinkage of the brain caused by dehydration cannot cause the constriction of the pial arteries and minute vessels. Reduction in the volume of the brain reduces the intracranial pressure. Reduced intracranial pressure causes a relative increase of pressure within the arteries, which would in fact tend to dilate them. The vessel diameter in all experiments returned to normal before the brain regained its bulk (fig. 4). The decrease in intracranial pressure apparently does not play any part in the pial vasoconstriction. As already mentioned, the

artery returned to its initial size while the intracranial pressure was still low. In experiment II (fig. 6), Ringer's solution was permitted to flow into the cisterna magna, so that the intracranial pressure was rapidly raised from 12 to the 100 mm. water level. The pial artery still continued to constrict.

The systemic arterial pressure rise after the injection of hypertonic dextrose solutions has been thought to be due to the increased blood

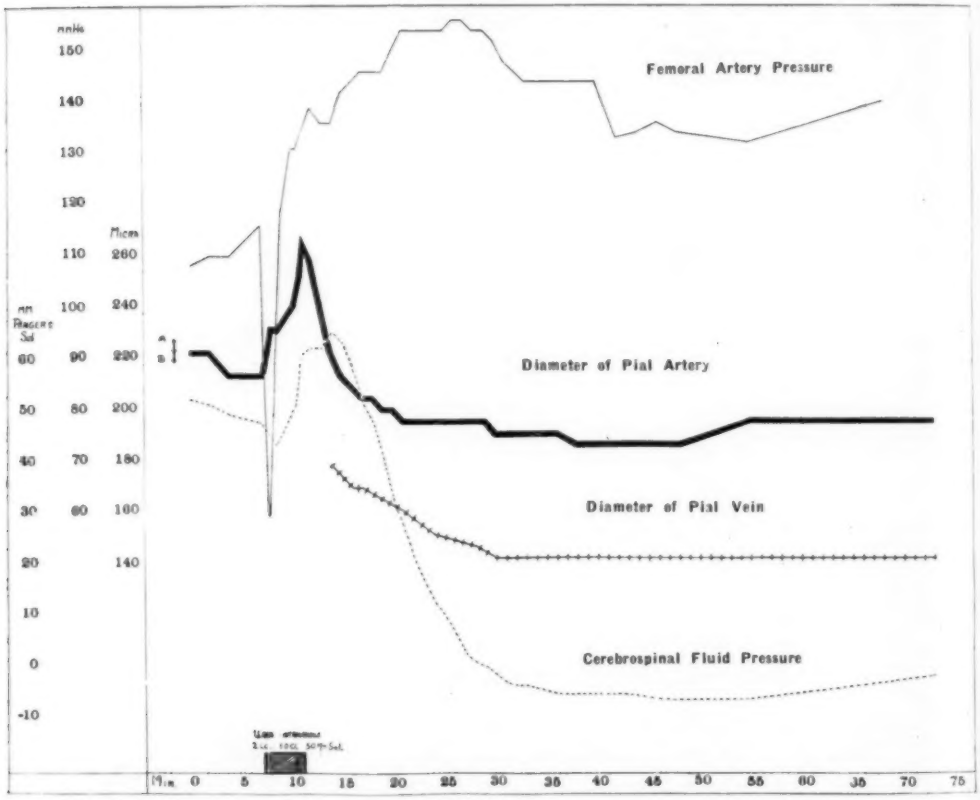
Femoral Artery Pressure
Diameter of Pial Artery
Diameter of Pial Vein
Cerebrospinal Fluid Pressure
Min 0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75

Fig. 5 (experiment III).—Action of urea administered intravenously.

volume and viscosity.[12] This, however, does not explain the pial vasoconstriction observed in these experiments.

The slight fall in the sagittal sinus venous pressure [7] after hypertonic solution might be considered a possible cause for reduction in the diameter of the pial artery. The lowered venous pressure might presumably decrease the capillary resistance and pressure, and this would decrease the pressure of the pial artery and thus permit constriction.

12. Berger, M., and Bauer, M.: Ztschr. f. d. ges. exper. Med. **49**:147, 1926.

But slight gradual variations in sagittal sinus pressure such as occur after injections of hypertonic solution have not resulted in changes in the diameter of the pial artery in control experiments.

The changes in the vessel could not result from activity of the vagus or depressor nerves, since a typical effect was noted after section of both vagi.

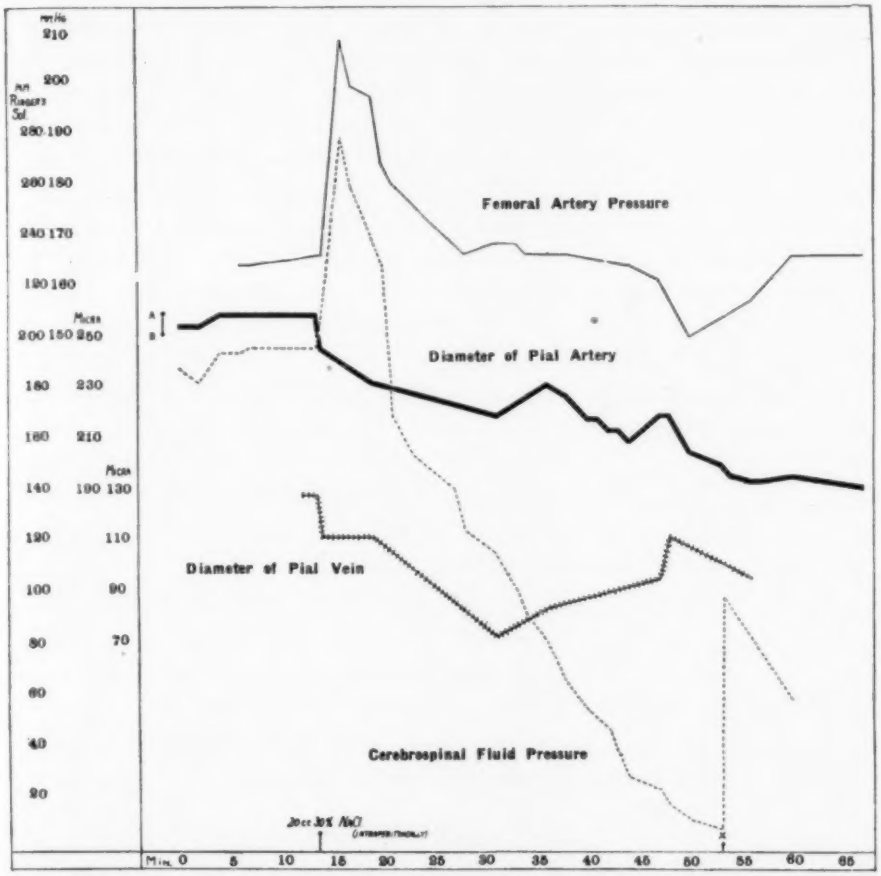
Femoral Artery Pressure
Diameter of Pial Artery
Diameter of Pial Vein
Cerebrospinal Fluid Pressure
Min. 0 5 10 15 20 25 30 35 40 45 50 55 60 65

Fig. 6 (experiment IV).—Action of sodium chloride administered intraperitoneally.

Coincident alteration in both cerebral and splanchnic vessels through effect on the central vasomotor regulatory apparatus seems improbable. Section of the cervical sympathetic nerves (one of the pial artery vasoconstrictors) did not reduce the effect of the hypertonic solution.

Direct effect of the altered osmotic pressure of the blood on the wall of the vessel seems the most likely explanation for the major portion of this alteration in diameter of the pial vessels. The exact

site of action, whether nerve endings, myoneural junctions, smooth muscle or endothelium, has not been determined.

These observations do not answer the question of whether the capillaries may not react independently of the larger pial arteries under extraordinary conditions of intracranial pressure. Cerebral capillaries may not always respond to a given stimulus as do pial arteries. It is possible that under some conditions they respond in the same way, under other conditions in an opposite way. If the stimulus affecting the lumen is not associated with great changes in intracranial (cerebrospinal fluid) pressure, the capillaries may change in diameter in the same direction as the pial artery. The hypertonic solutions, however, cause increased intravascular and decreased intracranial pressure; both tend to dilate the vessels. Even the combined effect of these pressures may conceivably be overcome by the strength of the arterial walls, but the capillary walls within the substance of the brain possess no such strength and offer practically no resistance to pressure from within or from without. For this reason it may be true that in response to hypertonic solutions the cerebral capillaries passively dilate. Evidence that capillary dilatation does actually occur under these circumstances is presented in part II.

CONCLUSIONS

1. Hypertonic solutions, injected into the blood stream or into the peritoneal cavity, are followed by constriction of pial blood vessels. Microscopic and photographic evidence of this is presented.

2. The increased osmotic tension of the blood seems to be the chief factor in causing this vasoconstriction.

3. The diameter of the pial artery is seen to alter independently of blood pressure and of intracranial pressure.

4. Among the various factors which regulate cerebral blood supply one must include changes in osmotic tension of the blood.

ABSTRACT OF DISCUSSION

DR. HOWARD C. NAFFZIGER, San Francisco: I am extremely interested in this work. There are some points about it that are not clear to me, perhaps that is the reason I do not feel that they are conclusive. I appreciate the fact that Riegel, Jolly, Nothnagel, Francke and others noted alterations in the caliber of the cerebral vessels, and that Leonard Hill and other English workers had subjected their conclusions to criticism because certain passive factors were not taken into account. Those passive factors consisted first, in having an open skull, second, that differences in systemic arterial pressure were not controlled, and third, they pointed out (particularly Leonard Hill) that venous pressures must be controlled. We know that when venous pressure is raised, as in the Queckenstedt test, by jugular compression, intracranial pressure is raised. When venous pressure is raised and kept up, then the intracranial pressure, the intra-arterial pressure in the small arteries and the intravenous pressure all tend to rise approaching the

pressure in the larger arteries. If there is a venous block or if there is a rise in venous pressure, there is a backing up which may or may not be expressed in the altered caliber of the arteries. Even with the arterial pressure of the body going in the other direction, we can necessarily assume that there are no passive factors.

It seems to me that in addition to the experiments here reported, there should be added the point as to whether an alteration in venous pressure precedes the change in the caliber in the arteries. Florey pointed out in his work on the brain two years ago that cerebral arteries on direct stimulation and with an open window did respond to mechanical, thermal, chemical and electrical stimulation. So far as I know, he did not go farther than that. He found that certain drugs had effects the opposite to those commonly supposed.

I have no doubt that Dr. Wolff has made some observations on the associated venous pressure, but it is not clear to me yet why he should assume that direct stimulation of the arteries through the nervous system is the sole factor accounting for the change in arteries, unless he has controlled venous pressure and has seen that an alteration in venous pressure did not precede the change in the arteries.

DR. WOLFF: I am grateful to Dr. Naffziger for bringing out these points. In our previously reported work on the innervation of cerebral arteries, but briefly reviewed here, we observed that stimulation of the left cervical sympathetic nerve resulted in constriction in the cerebral arteries. There was usually concomitant slight reduction in the cerebrospinal fluid pressure. To understand the influence of venous pressures on the size of cerebral arteries, we separated the cervical arteries from the veins and put a ligature around the neck so that much of the venous outflow was stopped. This always resulted in an increase in the cerebrospinal fluid pressure. We were able to determine that variations in pressure, similar in degree to those observed in the experiments on innervation (unless they were continued for a period much longer than our stimulation) did not have any effect on the size of the cerebral arteries. We felt then, from these controls, that such changes in venous pressures as were observed during the period of stimulation of the nerve were not responsible for changes in the size of the cerebral arteries. At first we did not care to open the head to take torcular pressures, because we would be dealing with an open box, the thing we wished to avoid. We later learned that it was possible to insert a needle into the sagittal sinus through a minimum bone defect, so that the cranium was still practically closed. By this means we observed, on stimulation of the sympathetic and vagus nerves, that changes in venous pressures did not necessarily always accompany changes in the caliber of the cerebral arteries. Certainly in these experiments, alterations in venous pressure could not be held responsible for alterations in the size of the cerebral arteries.

Artificial respiration was performed in several animals so that a definite, constant fluctuation in intrathoracic pressure might be maintained. One can readily alter the size of the cerebral arteries by increasing the intrathoracic pressure. The venous return to the heart is thus reduced and arterial pressure falls. This results in cerebral anemia and arterial dilatation, for cerebral anemia is always accompanied by vasodilatation.

These control experiments made us feel that we had a fair basis for our conclusions as far as venous pressures were concerned.

A STUDY OF THE SPINAL FLUID PRESSURE IN THE DIFFERENTIAL DIAGNOSIS OF DISEASES OF THE SPINAL CORD*

BYRON STOOKEY, M.D.
AND
DOROTHY KLENKE, M.D.
NEW YORK

The introduction of the lumbar manometric test [1] of the spinal fluid in the differential diagnosis of diseases of the spinal cord has led to a striking contrast in both the number of laminectomies performed and the pathologic processes found as compared with a similar period before this test had become a routine procedure. Many conditions formerly diagnosed as multiple sclerosis or other inoperable diseases of the spinal cord have been shown to be tumors of the spinal cord or other pathologic processes remediable by neurologic surgery. It is significant that during the three years from 1920 to 1922 inclusive, before the routine introduction of the lumbar manometric test, forty-three laminectomies were performed at the Neurological Institute; whereas during the years from 1924 to 1926 inclusive, when this test had become a routine procedure, ninety-four laminectomies were performed, an increase of 116 per cent. In each of these two three-year periods, the attending staff and methods of neurologic examination were essentially the same.

The lumbar manometric test has been an important factor in distinguishing operable from nonoperable conditions of the spinal cord. Unfortunately, the neurologic signs of intrinsic disease of the spinal cord so closely simulate the signs produced by neoplasms of the spinal cord or other operable lesions that differentiation on neurologic signs alone is frequently impossible. It is in these conditions that striking information is gained from the lumbar manometric test.

The result of studies of manometric tests in fifty suspected tumors of the spinal cord was reported by one of us [2] before the Association for Research in Nervous and Mental Diseases in 1924. To this report we are now adding the experience gained in the present series of 235 addi-

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* Read at the Fifty-Third Annual Meeting of the American Neurological Association, Atlantic City, N. J., May 26, 1927.

* From the Department of Neurosurgery, Neurological Institute, New York.

1. Stookey, B.; Merwarth, H., and Frantz, A.: Manometric Study of the Cerebrospinal Fluid in Suspected Spinal Cord Tumor, Surg. Gynec. Obst. **41**:429 (Oct.) 1925.

2. Stookey, B.; Merwarth, H. R., and Frantz, A. M.: A Manometric Study of the Cerebrospinal Fluid in Suspected Spinal Cord Tumors, Proc. A. Res. Nerv. & Ment. Dis., Dec. 29 and 30, 1924.

tional cases in which the lumber manometric test was made because neoplasms of the spinal cord were suspected. The information from this larger series has served to confirm our belief that this procedure is one of the most valuable in the differential diagnosis of diseases of the spinal cord.

REFINEMENTS IN PROCEDURE OF LUMBAR MANOMETRIC TEST AND TYPES OF OBSTRUCTION

Hilton [3] was the first to demonstrate the effects of compression of the jugular vein on the free flow of the cerebrospinal fluid in the subarachnoid space, as pointed out by Merwarth.[4]

> At an ordinary postmortem examination, with the body lying on its back, place a ligature tightly around the neck, so as to compress the jugular veins and prevent the venous blood from running out of them. Then remove the thoracic and abdominal viscera, and divide transversely and neatly the various veins which escape from the vertebral canal, through the intervertebral foramina, taking care to leave these veins full of blood. Then take away the bodies of the third and fourth lumbar vertebrae, so as to expose the vertebral canal—with a body so prepared, if the blood within the veins of the neck be pressed upwards through the internal jugular veins toward the interior of the head, it will be seen that just in proportion as you press the venous blood in that direction so you will observe the dura mater rise into the place from which you have removed the lumbar vertebrae, thus showing that as you push the venous blood into the interior of the unyielding cranium, you displace the cerebrospinal fluid. The evidence of the displacement being this, that you see the dura mater lifted up by the fluid at the part where you have removed the two lumbar vertebrae.
>
> Some years ago I had in Guy's Hospital a patient suffering from a fracture of the base of the skull, and from one of his ears a thin watery fluid was pretty constantly running. It occurred to me that if I could fill this patient's head full of venous blood, I might succeed in displacing the cerebrospinal fluid, and that if the fracture had established an easy communication between the auditory canal and the cerebrospinal fluid in the interior of the skull, I should be able to force out of the ear some of the cerebrospinal fluid. I accordingly told him to take a full breath; I then held his nose and lips and put my finger so as to compress his jugular veins on each side of his neck. His face became exceedingly congested and discolored and he commenced struggling to get rid of the pressure of my hands on his nose and mouth. This had scarcely taken place before a quantity of thin fluid came running out of the auditory canal and I succeeded in collecting nearly a half ounce.

Queckenstedt [5] first applied this test in the diagnosis of tumors of the spinal cord. He showed that in the presence of large tumors of the spinal cord deep compression of the jugular veins did not cause a rise in

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3. Hilton: Lecture on Rest and Pain, London, Bell and Daldy, 1863.

4. Merwarth, Harold: Read before the New York Neurological Society, April 12, 1927.

5. Queckenstedt: Zur Diagnose der Rückenmarkskompression, Deutsche Ztschr. f. Nervenh. **4**:325, 1916.

spinal fluid pressure. Since his contribution, refinements in the method and advances of technic have permitted finer degrees of differentiation with recognition of various types of obstruction other than the absolute block found only in the advanced conditions.

To make this test more accurate and to bring out finer details, both the rise and fall have been timed in five second intervals during the period of compression of the jugular veins and after their release. The importance of timing the duration of compression and of accurately charting the rise and fall of the fluid is obvious, if comparisons are to be made and finer changes detected. Compression of the jugular veins is done for ten seconds, and the rise is carefully noted. In a normal, free subarachnoid space the rise during this interval is prompt, reaching approximately from 300 to 400 or 500 mm. On release of pressure, there is then a prompt fall to, or nearly to, the original level within ten seconds. We, therefore, consider ten seconds our standard time for compression of the jugular veins. If the duration of compression varies, comparisons are less accurate, and finer details are lost. Charts, rather than numerical records of the changes in the rise and fall, render slight variations more apparent, and are, on the whole, more graphic. By charting our observations, we have been able to differentiate several forms of obstruction having definite clinical significance other than the absolute block demonstrated by Queckenstedt, which is present only in massive obstruction. By finer methods in performing the test, we recognize three types of obstruction:

1. Absolute block produced by an obstruction so complete that there is no rise on compression of the veins (fig. 3).

2. Complete block, produced by obstruction which nearly completely fills the subarachnoid space, yet permits a slight rise of pressure on deep compression (fig. 4).

3. The establishment of a new high level, the delayed fall or the delayed rise. In the establishment of a new level, the fluid rises promptly on deep compression but does not fall to the original level within a given period of time; in this type, a new level of from 100 to 200 mm. higher than the original level may be established, and the fluid may remain at this level for an appreciable time. In the delayed fall, deep compression causes a nearly normal rise, but release of compression of the jugular vein is followed by a delayed and often incomplete fall. In the delayed rise, the rise on deep compression does not begin instantly but only after the pressure has been exerted for a few seconds. The rise may then be rapid and the fall likewise prompt (figs. 5, 6 and 7).

In addition to the deep compression advocated by Queckenstedt, we have found that instantaneous touch compression of the jugular veins causes a rise of from 2 to 10 mm. in the pressure of the spinal fluid. Since this pressure is exerted for only an instant, reflex coughing, straining, or choking is avoided, consequently this test has not the drawbacks which may invalidate the readings during deep compression.

When the subarachnoid space is patent, instantaneous touch compression causes an immediately perceptible rise in the spinal fluid manometer, showing that the spinal fluid balance is delicate and responsive to the slightest increase in pressure. Only the cerebrospinal fluid manometer is delicate enough to demonstrate the finer changes. The manometer of Israel Strauss is most satisfactory. Neither the mercury manometer nor the air manometer introduced by Claude reveal these delicate variations. When using the spinal fluid manometer, finer variations in the pressure of the spinal fluid can be recognized.

Instantaneous touch compression causes a rise in pressure which is due only to the effects of compression of the jugular vein; consequently, in studying the patency of the subarachnoid space, this test adds valuable data to that obtained by deep compression. Instantaneous touch compression was found to cause both a prompt rise and fall in 82 per cent of the negative tests but no response was obtained in any of the positive tests. By noting the effects of instantaneous touch compression, it is possible to predicate whether deep compression will show an absolute block, a complete block, a hanging rise or fall, or an entirely negative reading. Instantaneous touch compression is of problematic value in the intermediate group of doubtful manometric tests.

To the foregoing procedures an additional phase, termed the pressure index, has been introduced. This was not in the original test described by Queckenstedt. By pressure index, we mean the ratio of the fall produced by the withdrawal of 7 cc. of fluid to the initial level. The initial cerebrospinal fluid pressure readings vary slightly in the various clinics, depending on the bore of the tube used to determine the pressure. The Israel Strauss manometer is the most satisfactory, since as the tube is calibrated in millimeters throughout its entire length, more accurate readings are possible. With the Strauss manometer the initial pressure has been between 100 and 110 mm., the initial pressure being approximately the same whether the subarachnoid space is free or blocked. We have had no difficulty in obtaining the initial pressure without using anything more than a two-way cock; thus the initial pressure can be obtained without loss of spinal fluid. All types of complicated apparatus have been discarded, since an apparent block may be recorded, when, as a matter of fact, lack of patency of some part of the appliance may produce a false reading. In suspected tumors of the spinal cord, we have not found that the loss of a few drops before the attachment of the manometer was significant. The simpler the appliance, the less is the danger of error. Comparison of the fall produced by the removal of approximately 7 cc. of cerebrospinal fluid with the initial pressure level offers significant evidence to indicate the patency or obstruction of the subarachnoid space. With a free subarachnoid space, the pressure level falls approximately 50 per cent or from 100 mm. to 50 mm., whereas

when the space is occluded the fall is often 100 per cent, that is, from the initial level to zero. The percentage fall for the positive manometric blocks was approximately 93 per cent of the initial pressure level, while the percentage fall for negatives was less than 50 per cent of the initial level. The pressure index is unfortunately of little value in those cases in which there is an initial level of less than 60 mm., since here the normal fall of approximately 50 mm. so reduces this pressure that it can no longer be read in the tube, and thus an apparent fall to zero is recorded.

In view of these important new additions to this test, the term lumbar manometric test is perhaps preferable to either the Hilton or the Queckenstedt test, because the complete lumbar manometric test includes new phases such as the instantaneous touch compression, the pressure index, the time element, the graphic representation of these phases, and recognition of the different types of block.

TECHNICAL DETAILS

The lumbar manometric test, to be of value, must be done with care, precision, and regard for a host of details which may modify the pressure readings. Careless technic will bring out only the most obvious total and absolute blocks. Even at the Neurological Institute, where the resident staff has presumably been trained in the technic of the test, variations in the test are found; fortunately, most of the errors can be controlled. However, in spite of careful training, we were forced to discard twenty-five charts from the series because the data were too inaccurate to permit interpretation. Forty-eight per cent of the discarded charts were recorded by one intern. Lack of interest and slovenly methods render this test valueless. In hospitals where the test is infrequently made, the results are often variable and depart so far from the type of charts with which we are familiar that interpretation is impossible. To discard the manometric test as unreliable under such circumstances would be as unreasonable as to discard the Wassermann test were it done by technicians who poured out unmeasured amounts of antigen and sensitizer, only guessing at the proportion required, instead of carefully measuring each.

If the lumbar manometric test is to be reliable, minute attention to details is essential. Factors most apt to invalidate the test or to lead to errors in its interpretation are:

1. The position of the head, which should be level with the spine.

2. The position of the neck, which should be straight, since if it is bent it will compress one of the jugular veins.

3. Relaxation of the patient, for if he strains or holds tightly on the bedding, etc., a false initial pressure level will be obtained.

4. Patency of the apparatus, which, if doubtful, should be tested by moving or rotating the needle, and by having the patient strain. If the arachnoid or a nerve root plug the lumen, no rise will be obtained.

RELATIVE VALUE OF THE LUMBAR MANOMETRIC AND IODIZED OIL TESTS

No purely mechanistic approach to accurate diagnosis of spinal cord neoplasms is possible. Neither the lumbar manometric test nor injection of 40 per cent iodized oil can replace a minute and accurate neurologic examination. They are only aids in the neurologic diagnosis. The manometric and iodized oil tests are abnormal only when the subarachnoid space is sufficiently compromised to cause obstruction to the passage of both the cerebrospinal fluid and the iodized oil. Although both the cerebrospinal fluid and the iodized oil may pass an incomplete obstruction, a careful and painstaking manometric study will show the manner in which the fluid passes the obstruction. The same may be said for iodized oil when its passage is followed with the fluoroscope. However, a special fluoroscopic table permitting the patient to be tilted is essential. Small intramedullary neoplasms, extradural ventral chondromas, and certain other forms of obstruction may show a negative manometric test and offer no block to the passage of iodized oil. Hence the final diagnosis rests on a careful neurologic examination and not on any mechanical device.

The real problem in the treatment of patients with tumors of the spinal cord is early diagnosis. Removal of the tumor before it has completely occluded the subarachnoid space and severely traumatized the spinal cord is important. When a tumor has attained such size that it causes massive obstruction to the subarachnoid space, the manometric and iodized oil tests are frequently only confirmatory; if carefully sought by those trained in neurologic diagnosis, the neurologic signs are usually sufficient to demonstrate the level. The value of these tests is to aid in distinguishing between intrinsic diseases of the spinal cord and expanding lesions of the cord or its membranes. Both may give rise to nearly identical neurologic signs, but, if patency of the subarachnoid space is proved, the differential diagnosis may be made more surely. The value of these special tests is not in determining the level, but in demonstrating the patency of the subarachnoid space. This is proved as well by the lumbar manometric test as by an injection of iodized oil. With this information, the differential diagnosis can be made by the neurologic examination. Such conditions as nonobstructive arachnoiditis and extradural ventral chondroma may show both a negative manometric and a negative iodized oil test, and yet the diagnosis may be established by the neurologic examination.

It is rather surprising to find in the literature a heading such as "Tumeur Intramédullaire-Lipio-Diagnostic" [6] . . . "Nous avons pu grâce au lipiodiagnostic sous-arachnoïdien, affirmer et localiser, . . . une néo-formation intramédullaire," whereas the appended histories and neurologic signs leave little doubt as to the diagnosis and the localization without injection of iodized oil.

INDICATIONS FOR COMBINED CISTERN AND LUMBAR PUNCTURE OR IODIZED OIL

When the lumbar manometric test is obviously and unquestionably negative, there is no indication for injection of iodized oil. When it is frankly positive, we likewise see no indication for injection of iodized oil, except in those rare cases in which the level cannot be determined by the neurologic observations. When the lumbar manometric test is doubtful, recourse to more elaborate procedures is indicated. Either combined puncture as advocated by Ayer [7] or an injection of iodized oil should be used. Both of these procedures are valuable and have a definite but well defined place in the diagnosis of diseases of the spinal cord. In 1923, when the present study was originally undertaken, an attempt was made to obtain all the information possible from the routine lumbar puncture, as it was felt that this procedure should be made to yield its fullest information. That it can be made to yield sufficient in the vast majority of cases has been amply demonstrated by our study. When the information gained is not sufficient, additional measures, such as combined cistern and lumbar puncture, should be used. We are not opposed to these measures, but have sought to define their indication.

The attempt to localize tumors of the cauda equina is perhaps the most positive indication for an injection of iodized oil. Here the situation is entirely opposite to that found in the spinal cord. Even the most competent neurologic examination frequently fails to determine the exact level of a tumor of the cauda equina. The injection of iodized oil through the lumbar needle can then be used, after a manometric test has shown the patency of the subarachnoid space above the lumbar needle. This, in our opinion, is the most important indication for the injection of iodized oil (fig. 1).

By successive punctures and manometric studies, interesting results have been obtained in localizing tumors between the first and fourth lumbar vertebrae. If a block is found with the needle between the fourth and fifth lumbar spines and none with the needle between the first and

6. Sicard; Robineau, and Haguenau: Rév. neurol. **1**:539, 1927.

7. Ayer, J. R.: Spinal Subarachnoid Block, as Determined by Combined Cistern and Lumbar Puncture, with Special Reference to the Early Diagnosis of Cord Tumor, Tr. Am. Neurol. A., 1921, p. 272.

second spines, a fairly limited localization of the tumor is made. However, if a more limited localization is desired, iodized oil may be injected, although it is not essential, since the intervening laminae would be removed in order to remove a tumor above the fourth lumbar vertebra.

DISCHARGE MANOMETRIC TEST

Before the patient is discharged, a postoperative manometric test should be performed when the return of function has been unusually slow, since occasionally, even after complete removal of an extradural tumor, a second unsuspected intradural tumor may have been overlooked.

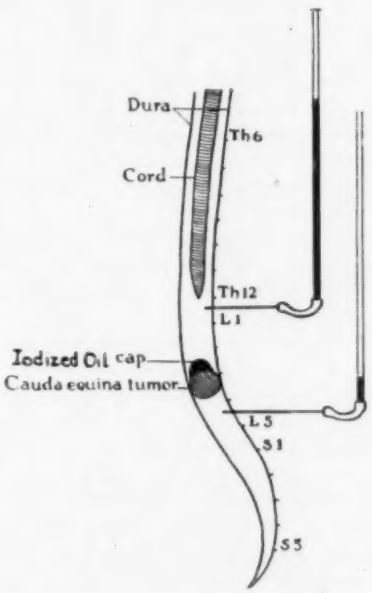

Fig. 1.—Schematic drawing indicating localization of a tumor of the cauda equina by double lumbar puncture. The upper needle demonstrates the patency of the subarachnoid space as far as the first lumbar vertebra. The lower needle shows a complete block above the fourth lumbar vertebra. Thus, by a double manometric test, an obstruction between the first and fourth lumbar vertebrae is localized. Iodized oil may be injected to verify the localization, but it is not necessary, since the intervening vertebrae would have to be removed for exposure.

The postoperative lumbar manometric test was of particular value in one such case. After the removal of a large extradural sarcoma, only a limited return of function occurred. A second lumbar manometric test showed complete block, and at operation a large intradural tumor totally unrelated to the extradural tumor was found. Prompt return of function took place and the second postoperative manometric test was entirely negative.

THREE PHASES TO EACH MANOMETRIC CHART

In interpreting the manometric observations, we recognize three phases in each test:

Phase A: The response to instantaneous touch compression.

Phase B: The character and manner of the rise and fall on deep compression.

Phase C: The pressure index obtained after removal of approximately 7 cc. of cerebrospinal fluid.

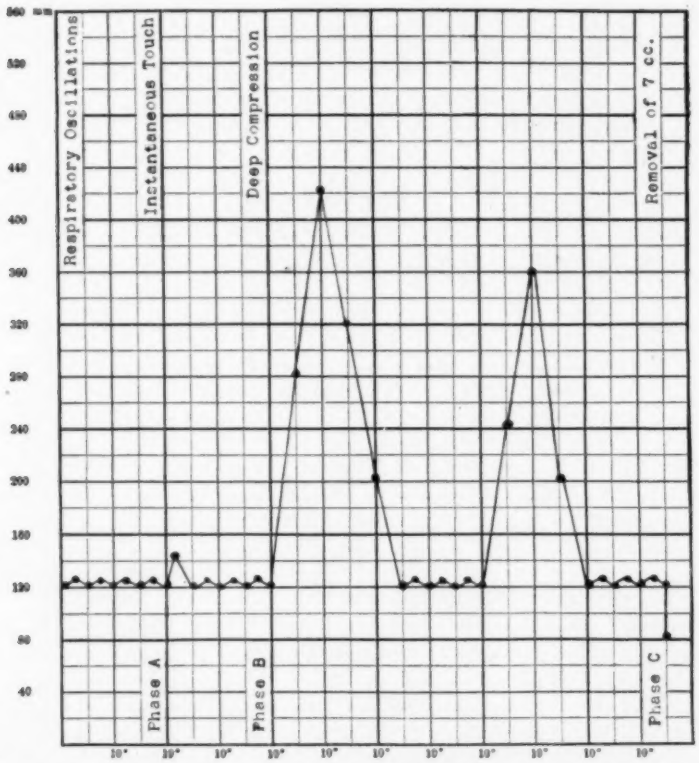

Fig. 2.—Negative manometric test. The fluid was clear and colorless. There was a rapid rise and fall after instantaneous touch compression, a high prompt rise and immediate complete fall after deep compression, and a fall of 40 mm., or 33 per cent, after the withdrawal of 7 cc. of fluid. Chemical analysis did not show a globulin excess and a total protein content of 22 mg. The clinical diagnosis was combined sclerosis with early pernicious anemia.

When all three phases show normal responses, the chart has been classified as negative (fig. 2). By normal we mean that phase A, instantaneous touch compression, shows an instantaneous rise of from 2 to 10 mm. with a rapid fall. Phase B, is normal when the rise on deep compression of the veins for ten seconds is immediate and continuous. The minimum rise during the ten second interval of deep compression of the veins is approximately 200 mm. The fall is as prompt as the rise;

the terminal part of the fall may be somewhat delayed but this is not considered of pathologic significance. Phase C, the pressure index, is the ratio of the amount of fall after the removal of 7 cc. of fluid to the original pressure level; this is normally about 50 per cent, or a fall of 50 mm.

Positive manometric charts show distinct changes in each of the three phases. Based on variations to these responses, we have been able to group the positive charts into three distinct types of obstruction.

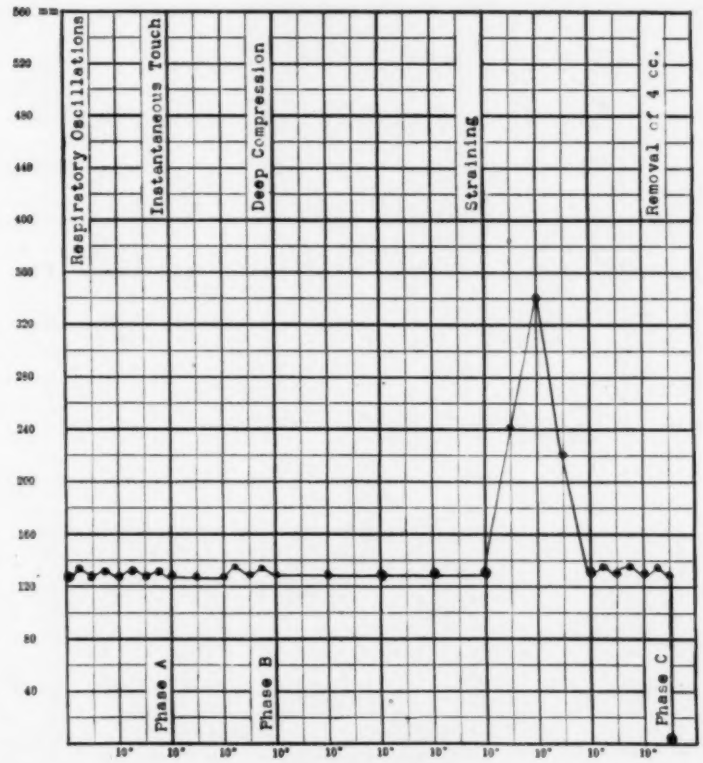

Fig. 3.—Positive manometric chart with an absolute block. The fluid was clear yellow. There was no rise after either instantaneous touch or deep compression, and a fall of 120 mm., or 100 per cent, after the withdrawal of only 4 cc. of fluid (no more could be obtained). Chemical analysis showed a globulin excess of 4 + and a total protein content of 300 mg. The postoperative diagnosis was an intradural melanosarcoma from the eight thoracic to the second lumbar vertebra.

We have called type 1 absolute block. This type does not show any rise in phase A or phase B, and has a fall of 100 per cent in phase C (fig. 3). Type 2, we have called complete block. This type may or may not show a slight response to phase A. Phase B, usually shows a slow and labored rise to a level approximately from 40 to

100 mm. higher than the initial level. Phase C shows a greatly increased fall (fig. 4). Unless the time element is considered and the results are graphically charted, this form is likely to be classed by some as negative, since the rise on deep compression, although slight, is definite; but in our experience this type of chart is as significant of block as are those charts which show an absolute block.

Included in type 3 are three types: the establishment of a new high level, the delayed fall, and the delayed rise. The most common is the

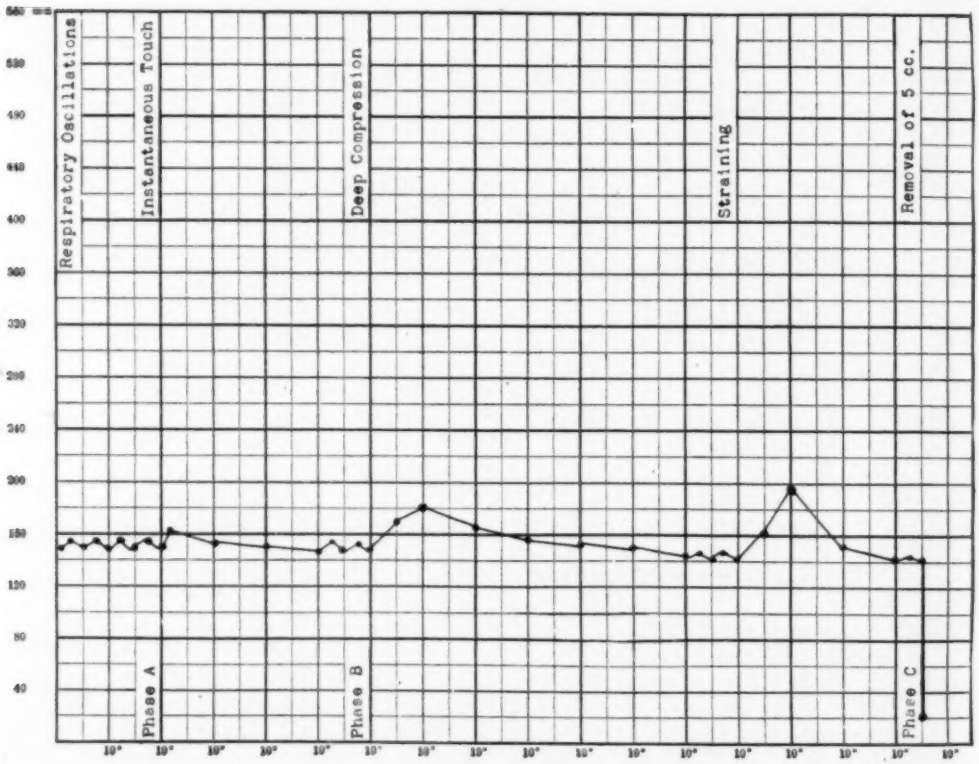

Fig. 4.—Positive manometric test with a complete block and some rise on compression of the jugular vein. The fluid was clear yellow. There was a low labored rise with a slow fall after both instantaneous touch and deep compression, and a fall of 110 mm., or 78 per cent, after the withdrawal of 7 cc. Chemical analysis could not be made as the fluid was bloody. The postoperative diagnosis was intradural sarcoma of cauda and conus.

establishment of a new high level (fig. 5). In this form, a new high level is maintained after each instantaneous touch compression instead of an immediate return to the original level after touch compression in phase A. The same phenomenon is seen on deep compression in phase B, the level on release of the pressure may be from 100 to 200 mm. higher than the original level. Phase C generally shows a fall to zero

after the removal of the fluid. The delayed fall is another indication of obstruction. It is seen in those cases after instantaneous touch and deep compression in which the return to the original level occurs slowly and hesitatingly. The fall after removal of fluid is greatly increased (fig. 6). Cases showing a delayed rise are less frequently seen, are less significant, and their interpretation is open to some doubt. They are not characterized by any response to instantaneous touch compression and have an initial delay in rise of the spinal fluid pressure on deep com-

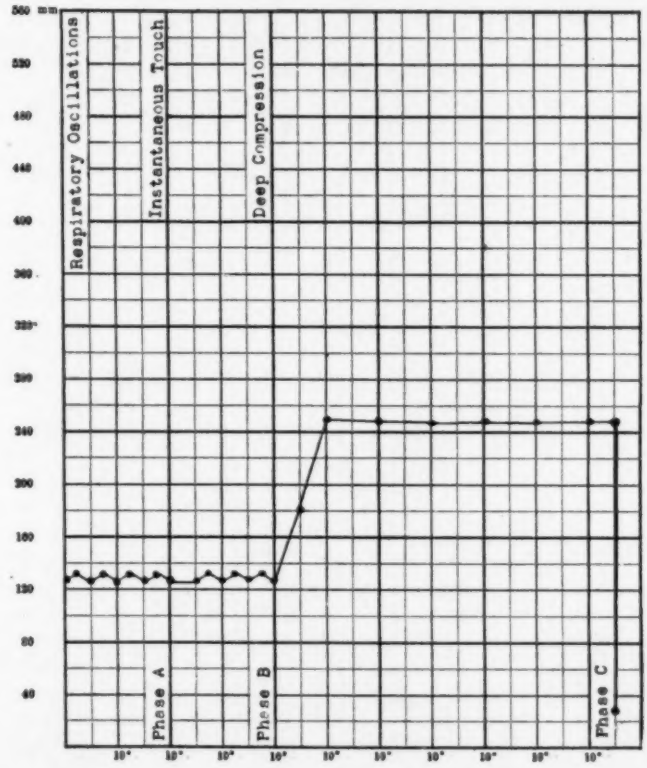

Fig. 5.—Positive manometric test with the establishment of a new high level. The fluid was clear yellow. There was no rise on instantaneous touch compression, a low labored rise followed by the establishment of a new high level after deep compression, and a fall of 220 mm., or 88 per cent, after the withdrawal of only 4 cc. of fluid (all that could be obtained). Chemical analysis showed a globulin excess of 3+ and a total protein content of 236 mg. The postoperative diagnosis was an intradural extramedullary endothelioma, opposite the sixth thoracic vertebra.

pression. No rise may occur for the first five or six seconds of deep compression, and then a sudden rise may occur as if the fluid had suddenly made its way past an obstruction. This rise may be approximately 200 mm. within the final second or two. Phase C may show a marked fall from the initial pressure level (fig. 7).

Responses of this kind are readily understood when the mechanics of the cerebrospinal fluid system are visualized. When a hanging fall with the establishment of a new high level is found, the obstruction to the return flow is complete. By pressure on the jugular veins, fluid under positive pressure has been forced past the tumor, but it cannot return when compression is released. An increased quantity of fluid is therefore held below the tumor with a consequent increase in the pressure of the subarachnoid space below the tumor, producing a new

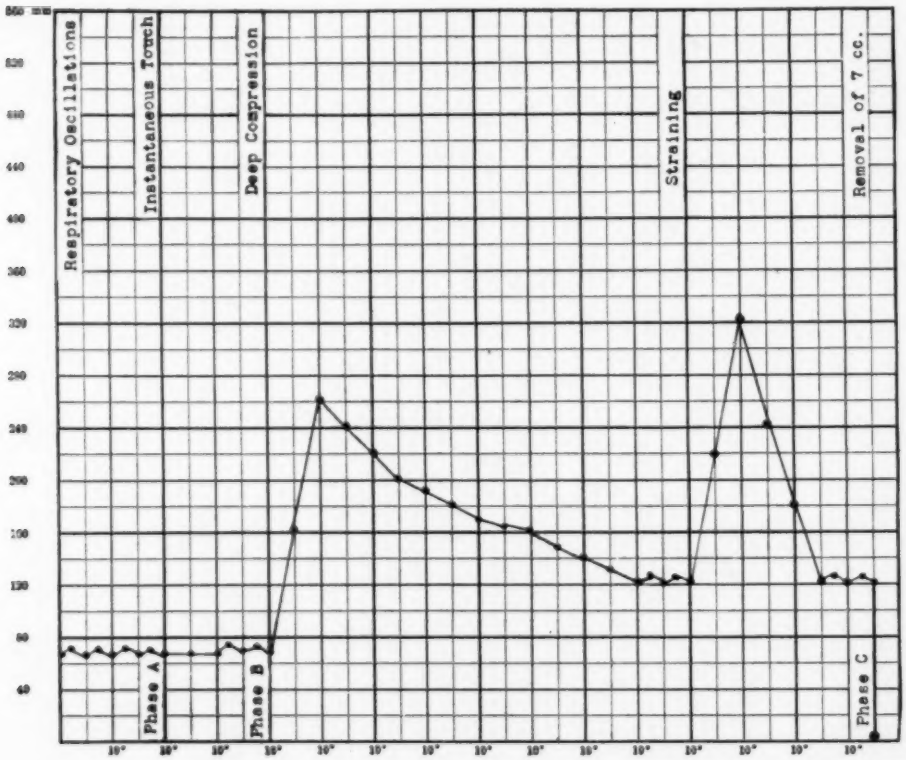

Fig. 6.—Positive manometric test with delayed fall. The fluid was clear and colorless. There was no rise on instantaneous touch compression, a normal rise with a delayed incomplete fall after deep compression and a fall of 120 mm., or 100 per cent, after the withdrawal of 7 cc. of fluid. The chemistry showed a globulin excess of 1 + and a protein content of 44 mg. The clinical diagnosis was a tuberculous kyphosis of the ninth thoracic vertebra.

high level (fig. 8). A delayed fall is due to an incomplete obstruction to the return flow of the fluid. The fluid forced past the tumor, no longer under the increased pressure due to compression of the jugular veins, seeps slowly upward past the tumor since the free return of the fluid is partially obstructed by the position of the tumor (fig. 9). When a tumor nearly completely fills the subarachnoid space and fluid is forced

against it with sudden impact, as is done on deep compression of the jugular vein, no rise may occur at first; but, after pressure has been exerted a short time, the fluid may squirt past the tumor either by finding a point of egress or by shifting the position of the tumor. Thus a delay in response followed by a sudden rise is seen (fig. 10).

Intermediate between the positive and the negative manometric tests is a group in which the responses are often such that they cannot be classified as either positive or negative. These we have termed doubtful

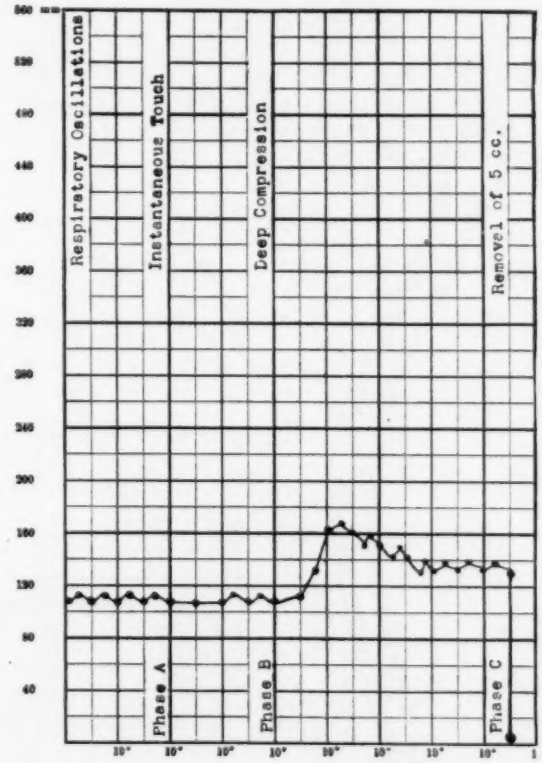

Fig. 7.—Positive manometric test with a delayed rise. The fluid was clear yellow. There was no rise. On instantaneous touch compression, there was a greatly delayed labored rise with a slow incomplete fall after deep compression, and a fall of 140 mm., or 100 per cent, after the withdrawal of only 5 cc. of fluid. Chemical analysis showed a globulin excess of 3+ and a protein content of 300 mg. The postoperative diagnosis was an intradural extramedullary endothelioma, opposite the second thoracic vertebra.

manometric charts, and have recommended that if the neurologic examination warrant further investigation, the manometric test be repeated and a double puncture done, or, if indicated, iodized oil be injected (fig. 11).

LUMBAR MANOMETRIC TEST ROUTINE WHEN SPINAL CORD NEOPLASM IS SUSPECTED

We have studied 235 lumbar manometric charts in the present series, excluding those reported in 1925. Many of the charts were made and interpreted before we had made the neurologic examination. It has been our custom to make the manometric test as frequently as possible

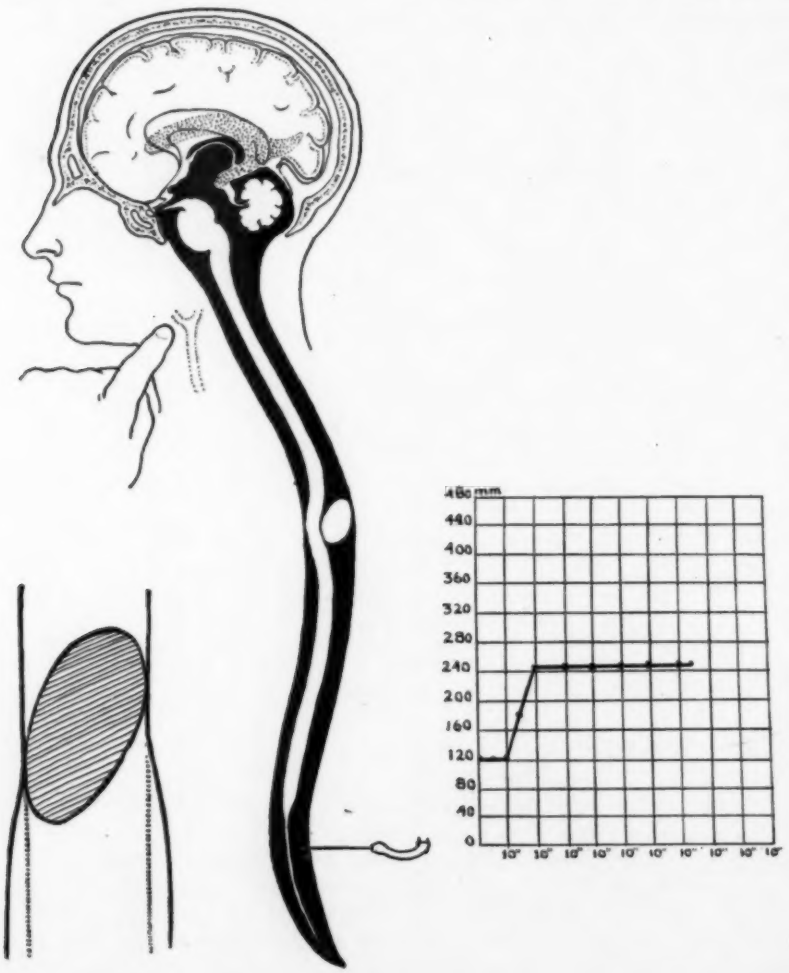

Fig. 8.—Schematic drawing indicating mechanism causing the establishment of a new high level, in a positive manometric test. By compression of the jugular vein, fluid under positive pressure has been forced caudal to the tumor. Release of the compression of the jugular vein removes the positive pressure on the fluid. The fluid caudal to the tumor is pocketed and unable to return. The lumbar sac is distended by the fluid forced past the tumor. The increased pressure of the lumbar fluid produces and maintains the new high level.

while still in complete ignorance of the history, the neurologic signs or the diagnosis in order to reach an unbiased opinion. In this way, the interpretation of the manometric observations is made on the manometric reading alone without reference to the clinical picture. The tests included in this series were made on patients whose symptomatology suggested diseases of the spinal cord. The large number of routine

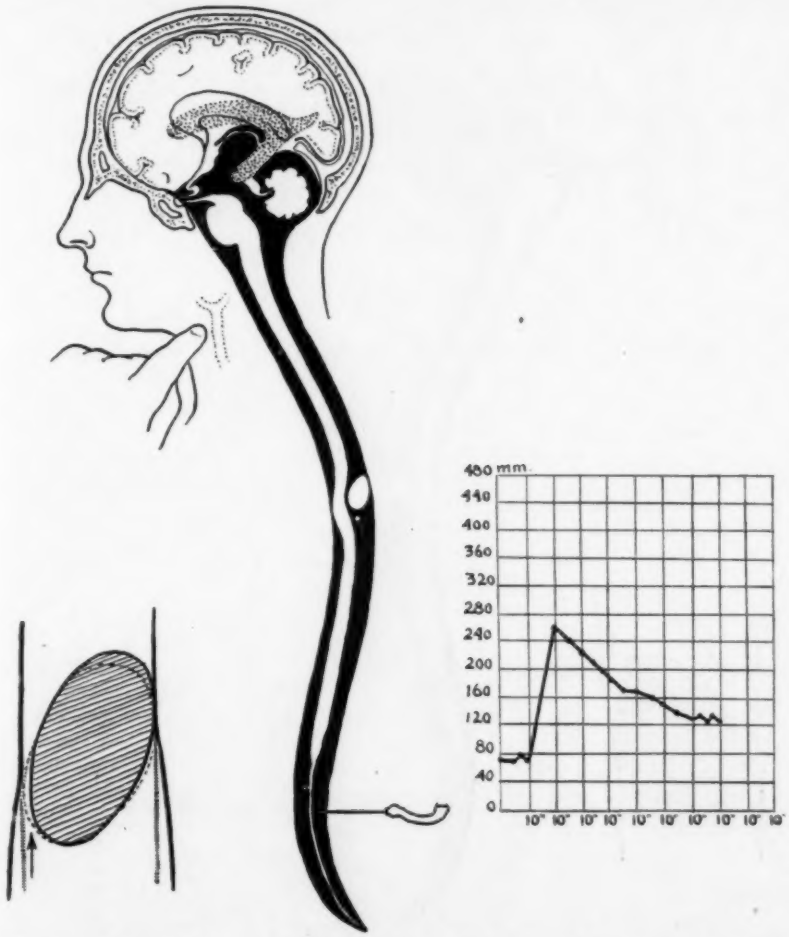

Fig. 9.—Schematic drawing indicating mechanism causing a prompt rise but delayed fall in a positive manometric test. The same mechanism is seen here as in figure 2, except that the fluid here can slowly seep past the tumor as it is not completely pocketed, hence the slow fall in the pressure after release of compression of the jugular vein.

manometric tests performed on patients not thought to have any disease of the spinal cord has not been included in this discussion. Of our series, there were 125 cases with negative, fifty-eight with positive and twenty-

seven with doubtful lumbar manometric tests; twenty-five charts were discarded.

NEGATIVE LUMBAR MANOMETRIC TESTS

Ten of the 125 patients with negative manometric tests were operated on, in spite of the negative manometric observations. It is interest-

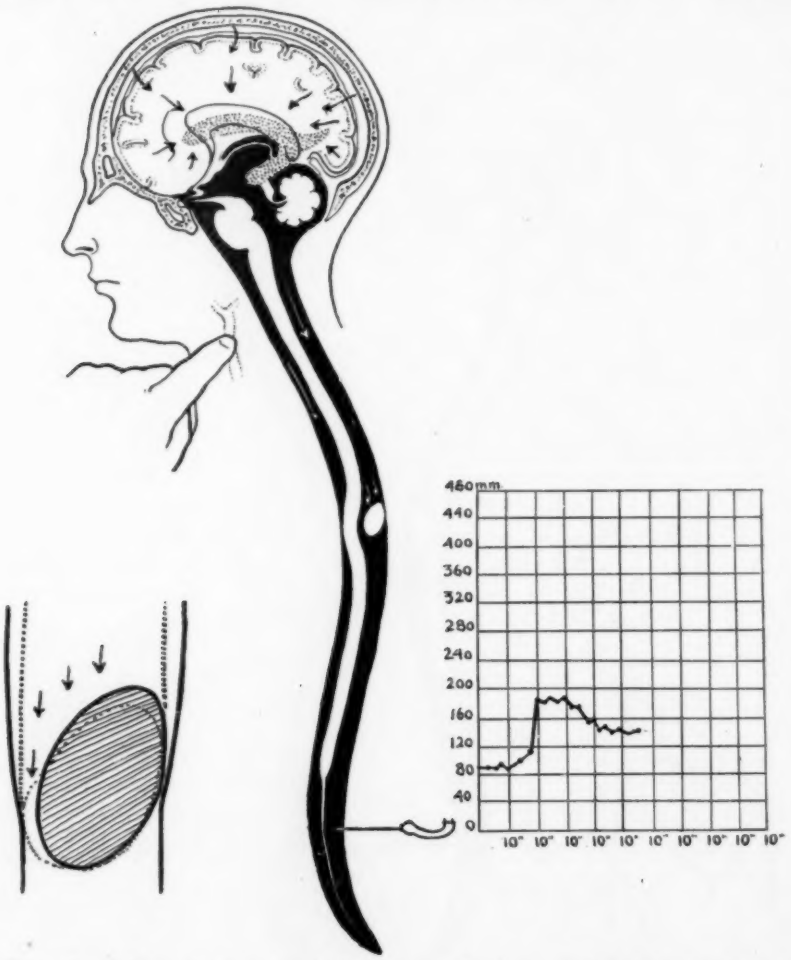

Fig. 10.—Schematic drawing indicating mechanism causing delayed rise in a positive manometric test. The impact of the fluid against the tumor is at first not sufficient to force it past the tumor, but after a few movements of continued pressure, the tumor is displaced sufficiently to permit the fluid to squirt past. Thus a delayed but definite rise of the fluid in the manometer occurs.

ing that not one of these patients showed any mechanical factors which seriously compromised the subarachnoid space, thus verifying the correctness of the interpretation of the manometric test which indicated a patent subarachnoid space. Two patients showed symmetrical enlarge-

ment of the spinal cord with a presumptive diagnosis of intramedullary cord neoplasm; as cord tissue can unfortunately not be taken for pathologic diagnosis, we frequently are forced to be content with the presumptive diagnosis of intramedullary neoplasm. Four of the patients on whom an exploratory incision was made showed so-called "atrophy" of the cord; another had a condition diagnosed as intramedullary gliosis; another radiculitis of the cauda equina, and two did not show any gross evidence of pathologic changes.

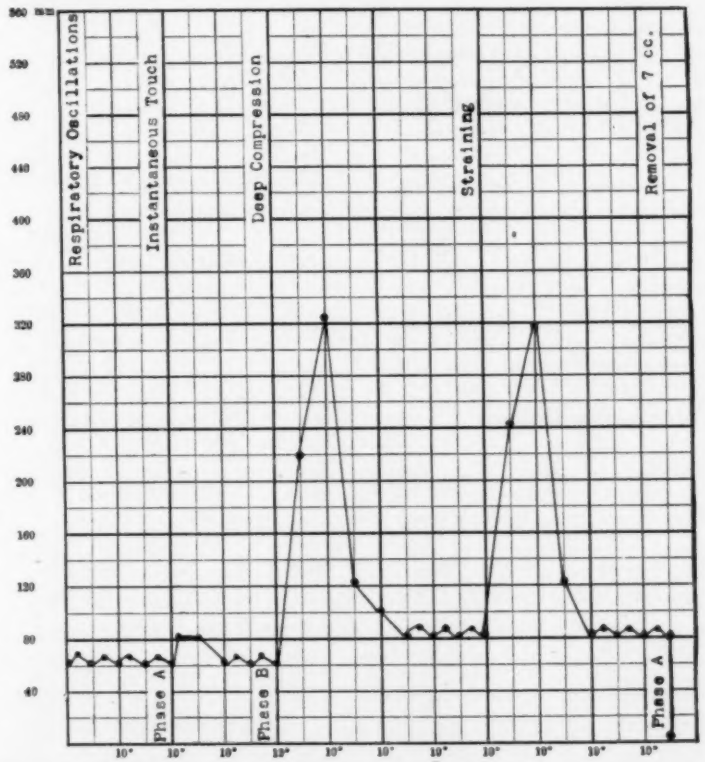

Fig. 11.—Doubtful manometric test. The fluid was clear and colorless. There was a rapid rise with a delayed fall on instantaneous touch compression, a normal rise and fall after deep compression, and a fall of 80 mm., or 100 per cent, after the withdrawal of 7 cc. of fluid. (Phases A and C were both abnormal.) Chemical analysis showed a globulin excess of 1 + and a total protein content of 45 mg. (both slightly increased). The clinical diagnosis was multiple sclerosis.

A negative lumbar manometric test may be found in the presence of an early intramedullary tumor of the spinal cord or a small extradural chondroma. As either of these may exist without obstructing the subarachnoid space, a negative test is rather to be expected. Since in either of these conditions, the iodized oil test may also be negative, the final

decision as to the diagnosis depends not on any one procedure, but on the complete record and especially on a thorough and minute neurologic examination.

POSITIVE LUMBAR MANOMETRIC TESTS

Of the fifty-eight patients with positive lumbar manometric tests, forty-four were operated on, and in each verification of the obstruction demonstrated by the manometric study was obtained. The following pathologic conditions were found:

Extradural tumors	14
Intradural tumors	18
Hydromyelia, with cord completely filling the subarachnoid space	2
Obstructive adhesive arachnoiditis	7
Extradural tubercular mass	1
Fracture dislocations	2

TABLE 1.—*Segmental Distribution of Tumors Causing Absolute Block*

Case	Tumor Type	Age	Duration of Symptoms	Segmental Level	Size
E. A.	Paravertebral chondroma	56	7 months	Thoracic X	3 × 5 × 8
M. S.	Extradural sarcoma	52	3 months	Thoracic II, VII	Extensive
G. A.	Extradural ventral chondroma	68	5 months	Cervical III	1 × 1 × 5
B. P.	Extradural neurofibroma	26	?	Thoracic I, II	1 × 2 × 1.5
P. N.	Extradural fibroblastoma	56	5 months	Thoracic IX, X	2 × 0.5 × 6
L. G.	Extradural fibrosarcoma	30	4 years	Thoracic II, IV	3 × 2 × 1
W. M.	Extradural adenocarcinoma	51	10 months	Thoracic IV	6 × 3 × 2
R. S.	Intradural melanosarcoma	49	3 years	Thoracic VIII, lumbar II	Extensive
S. A.	Intradural fibrosarcoma	45	8 months	Thoracic II, IV	3.5 × 0.5 × 0.5
A. J.	Intramedullary tumor	61	15 years	Thoracic I, II	2 cm. long
H. C.	Intramedullary tumor	20	2½ years	Cervical V, VIII	?

Extramedullary tumors tend to obstruct the subarachnoid space earlier than do intramedullary tumors, since the latter tend to grow in a cephalocaudad direction and do not close off the space until the cord has become symmetrically enlarged over a number of segments. However, when intramedullary tumors do occlude the subarachnoid space, it is likely to be closed off more completely, and the block is more likely to be absolute with marked disturbance in the venous circulation, yellow fluid and a high total protein content. The tumor type and the segmental level of the tumor are not the determining factors in producing subarachnoid block; block is due to the size of the tumor and the mechanical effects it produces (tables 1, 2 and 3).

Fourteen patients who showed subarachnoid block were not operated on. One, with a condition diagnosed as von Recklinghausen's disease, had previously been operated on and four discrete neurofibromas had been removed. On readmission to the hospital some time later, another block was demonstrated, but, as a second operation was not considered advisable, verification of this obstruction could not be obtained. It is

likely that additional tumors were present, for typical von Recklinghausen's disease had previously been found. Three of the remaining patients who were not operated on proved to have syphilis and improved on antisyphilitic medication. Another patient had a condition diagnosed as Pott's disease and an operation consequently was not performed. The remaining nine patients were thought to have tumors but were not operated on either because operation was refused, or because unanimity of opinion was lacking.

TABLE 2.—*Segmental Distribution of Tumors Causing Complete Block with Slight Rise*

Case	Tumor Type	Age	Duration of Symptoms	Segmental Level	Size
L. G.	Extradural neurofibroma.....	33	4 months	Thoracic X	4 × 2 × 1.5
J. M.	Extradural sarcoma.....	32	1 month	Thoracic VI	?
J. D.	Extradural ventral chondroma..	49	3 years	Cervical IV	3 × 4
C. M.	Extradural ventral chondroma..	63	3 years	Thoracic VIII, IX	4 × 2
L. B.	Intradural endothelioma.....	60	3 years	Thoracic IV	2.5 × 1
R. S.	Intradural endothelioma.....	13	3 years	Lumbar III	2 × 3 × 4
J. M.	Intradural endothelioma.....	47	2½ years	Thoracic XII, L, II	2 × 2.5 × 4
K. O.	Intradural neurofibroma.....	49	3 years	Cervical I, II	2.5 × 3 × 2
O. Z.	Intradural neurofibroma.....	48	8 months	Thoracic X	2.5 × 3
L. G.	Intradural fibrosarcoma.....	30	4 years	Thoracic II, IV	No report
M. F.	Intradural fibrosarcoma.....	42	6 months	Cervical II, III	3 × 3

TABLE 3.—*Segmental Distribution of Tumors Causing a Block with Hanging Rise*

Case	Tumor Type	Age	Duration of Symptoms	Segmental Level	Size
M. Z.	Extradural myeloma.....	50	15 months	Thoracic XII	Extensive
J. P.	Intradural neurofibroma.....	32	2 years	Cervical III	1.5 × 1.5 × 1
J. S.	Intradural neurofibroma.....	56	2 years	Thoracic VIII, IX	2 × 1 × 1
F. Z.	Intradural endothelioma.....	56	9 years	Thoracic IX, X	1.5 × 3 × 1
B. W.	Intradural endothelioma.....	62	10 months	Thoracic VI, VII	?
C. R.	Intradural fibroblastoma.....	35	1 year	Thoracic X	3 × 1 × 1
S. T.	Intramedullary ependymoma....	51	5 years	Thoracic III, IV	Cord filled entire subarachnoid space

DOUBTFUL LUMBAR MANOMETRIC CHARTS

An intermediate group in which the tests were inconclusive, with doubtful responses in one or more phases were found. A comparative analysis of the three phases in this group with those showing completely negative responses is seen in tables 4, 5 and 6.

The response to instantaneous touch compression was abnormal in 9 per cent of the negative charts as compared with 87 per cent of the doubtful. Deep compression showed normal responses in all the negative charts, whereas variations from the normal responses were found in 50 per cent of the doubtful charts. The pressure index showed increased fall in 28 per cent of the negative and in 48 per cent of the doubtful charts. These variations were sufficiently atypical to make it impossible

to consider the charts either frankly negative or frankly positive (tables 4, 5 and 6).

With doubtful manometric charts and inconclusive neurologic examination tests, combined lumbar and cistern puncture is recommended. This recommendation was made in only about 10 per cent of the cases in this series. When both the neurologic examination and the manometric

TABLE 4.—*Observations in Negative Charts*

	Cases Reported	Normal		Abnormal	
		Cases	Per Cent	Cases	Per Cent
Touch compression	110	100	91	10	9
Deep compression	125	125	100	0	0
Pressure index	88	64	72	24	28
Color	125	120	96	5	4
Globulin	114	108	96	6	4
Protein content	87	76	87	11	13

TABLE 5.—*Observations in Questionable Charts*

	Cases Reported	Normal		Abnormal	
		Cases	Per Cent	Cases	Per Cent
Touch compression	30	4	13	26	87
Deep compression	30	15	50	15	50
Pressure index	23	12	52	11	48
Color	30	28	93	2	7
Globulin excess	24	15	62	9	38
Protein content	10	3	30	7	70

TABLE 6.—*A Comparison of Tables 4 and 5*

	Negative Manometric Tests, per Cent	Questionable Manometric Tests, per Cent
Touch compression normal in	91	13
Deep compression normal in	100	50
Pressure index normal in	72	52
Color normal in	96	93
Globulin normal in	99	62
Protein content normal in	87	30

tests were equivocal, the diagnoses established were: intramedullary disease of the cord, multiple sclerosis, cerebrospinal syphilis, syringomyelia, and poliomyelitis. In some instances, though the manometric test could not be considered either frankly positive or entirely negative, the neurologic signs alone were enough to warrant operation. There were four such cases; in these, the postoperative diagnoses were: one intramedullary neoplasm with a symmetrically slightly enlarged cord; one small intradural neurofibroma, and two adhesive arachnoiditis without subarachnoid obstruction.

With doubtful manometric readings either combined cistern and lumbar puncture, as advocated by Ayer, or the injection of iodized oil is indicated.

THE PROTEIN CONTENT OF THE CEREBROSPINAL FLUID: ITS SOURCE AND DIAGNOSTIC VALUE

While the chemistry of the cerebrospinal fluid is not strictly one of the phases of the manometric test, we have usually considered it the fourth phase. The total protein content is of great significance in doubtful cases in throwing the balance either for or against further special studies. If the neurologic examination and the manometric tests are equivocal and the total protein content is slightly above normal, then combined puncture is indicated. An increase in the total protein content, i.e., over 50 mg., according to the method used by Ayer and Fremont Smith, was found in 78 per cent of the cases showing positive blocks, and was present in only 12 per cent of the fluids showing negative manometric examination. If the obstructive form of adhesive arachnoiditis, which characteristically may produce a block without an increase in the total protein, be excluded, then the percentage of subarachnoid block with an increase in the total protein content is raised from 78 to 95 per cent. An increased total protein content of the cerebrospinal fluid consequently bears a definite relation to obstruction of the subarachnoid space when this obstruction is due to compression.

Adhesive arachnoiditis, either diffuse or circumscribed, as pointed out by one of us in a previous report,[8] may cause either partial or complete subarachnoid block and yet be unaccompanied by any increase in the total protein content. Adhesive arachnoiditis offers, as it were, an almost ideal set of experimental conditions, designed to prove that obstruction of the subarachnoid space may occur without any increase in the total protein content, providing the circulation of the cord is not interfered with. In this condition, complete obstruction of the cerebrospinal fluid flow may be found without any apparent change in the circulatory condition of the cord. This confirms Mestrezat's [9] view that the increase of total protein content is the result of venous obstruction and diapedesis within the subarachnoid space. Stasis and diapedesis in compression are necessary to produce an increase in the total protein content of the cerebrospinal fluid, and therefore the total protein content is not increased in adhesive arachnoiditis.

The increase in the total protein content of the cerebrospinal fluid varies with the duration and the degree of the compression, and not with the nature of the compression, whether tumor or fracture. A

8. Stookey, B.: Adhesive Spinal Arachnoiditis Simulating Spinal Cord Tumor, Arch. Neurol. & Psychiat. **17**:151 (Feb.) 1927.

9. Mestrezat, W.: Le liquide céphalo-rachidien normal et pathologique, Paris, A. Maloine, 1912.

total protein content of 280 mg. was found in intradural extramedullary tumors and of 265 mg. in extradural compression of the cord due either to tuberculosis or to fracture dislocation without tumor. A total protein content of 80 mg. was found in extradural tumors and of 85 mg. in intramedullary tumors. In the inflammatory diseases of the cord, a total protein content of 100 mg. was found in cerebrospinal syphilis, and of 75 mg. in acute inflammatory diseases. If the compression has been of long duration, the protein content is greater than if the compression is of shorter duration. No relation could be established between the total protein content and the type of tumor. A high total protein content was found in intradural tumors as well as in extradural compression without tumor. In extradural compression without tumor, practically as high

TABLE 7.—*Protein Content*

Type Chart	Cases Reported	Normal (0-40 mg.)		Increased (over 41 mg.)	
		Cases	Per Cent	Cases	Per Cent
Negative	87	76	88	11	12
Positive	26	6	22	20	78
Doubtful	10	3	30	7	70

TABLE 8.—*Globulin Excess*

Type Chart	Cases Reported	No Excess 1+		2+		3+ and 4+	
		Cases	Per Cent	Cases	Per Cent	Cases	Per Cent
Negative	113	108	95	4	4	1	1
Positive	48	19	39	9	19	20	42
Doubtful	25	21	84	1	4	3	12

a total protein content was found as when the compression was due to an intradural tumor.

In extradural compression, two membranes, an intact dura and arachnoid, intervene between the compression and the cerebrospinal fluid; hence an increase in the total protein content of the cerebrospinal fluid cannot be interpreted as a special product of tumor metabolism, for this substance would have to pass through both the dura and the arachnoid to enter the cerebrospinal fluid. Furthermore, marked increase in the total protein is found when compression is due to fracture of the vertebrae without tumor formation. The increased total protein content, therefore, is not formed by metabolic products of the tumor. *It is directly proportional to the duration and the degree of the compression irrespective of the nature of the compression.* A positive block and increased total protein were found in the following pathologic conditions verified at operation: four extradural tumors, seven intradural extramedullary tumors, one intramedullary tumor, two fracture dislocations of the vertebrae with compression of the cord, one extradural tuberculous

mass, and one case of acute inflammatory disease of the cord. The diagnoses in the nonoperative cases in which were present both a positive block and an increased total protein were tuberculosis kyphosis, cerebrospinal syphilis and suspected spinal cord tumor.

RELATION OF GLOBULIN OF THE CEREBROSPINAL FLUID TO TOTAL PROTEIN CONTENT IN COMPRESSION

The globulin content, while not identical in its relationship to the total protein content, is closely parallel to it. Ninety-five per cent of the negative manometric tests did not show any or only a 1 plus globulin excess, while only 1 per cent of the negative manometric tests showed a 3 plus globulin excess (a case of cerebrospinal syphilis). None of the negative manometric tests showed a 4 plus globulin excess. No globulin

TABLE 9.—*Color Chart*

Type Chart	Cases Reported	Colorless		Yellow Fluid	
		Cases	Per Cent	Cases	Per Cent
Negative	125	120	96	5	4
Positive	58	37	64	21	36
Doubtful	27	25	93	2	7

TABLE 10.—*Summary of Chemistry*

	Increased Protein, per Cent	Increased Globulin, per Cent	Xanchrochromia, per Cent
Negative	12	1	4
Positive (exclusive of adhesive arachnoiditis)	95	80	55

excess or only a 1 plus excess was found in 39 per cent of the patients with a positive block, while a 3 or 4 plus globulin excess was found in 42 per cent of these. A 3 or 4 plus globulin excess was found in five patients with extradural tumors, in twelve with intradural tumors, in one with fracture dislocation, in one with an extradural tuberculous mass, and in one suspected of having a tumor of the spinal cord. Operation was not performed on any of these patients. Here again the globulin excess in compression of the spinal cord was found to be dependent, as is the total protein content or xanthrochromia, on the duration and degree of compression rather than on the nature of the compression.

XANTHROCHROMIA

Change in the color of the cerebrospinal fluid occurs far less frequently than an increase in protein or globulin. Xanthrochromia with block usually indicates complete subarachnoid obstruction. The presence of clear colorless fluid does not, however, militate against the complete-

ness of such block. Xanthrochromia is usually present in complete block of long standing. A complete obstruction which has existed for a long time is more apt to produce xanthrochromia than one equally complete which has been present for a shorter time. Xanthrochromia occurred in 7 per cent of the doubtful manometric tests, in 4 per cent of the negative tests, and in 36 per cent of the positive blocks. It occurred in intradural extramedullary neoplasms, in massive extradural compressions (fracture dislocation of the vertebrae) and in large intramedullary neoplasms, as well as inflammatory diseases.

The colloidal gold curve in the negative and positive manometric tests did not show any relationship to the obstruction or freedom of the flow of subarachnoid fluid, nor did it indicate the presence or absence of a tumor. It corresponded to the Wassermann reaction.

CONCLUSIONS

1. The lumbar manometric test should be a routine procedure whenever disease of the spinal cord is suspected.

2. New factors have been developed in the technic of the lumbar manometric test not in the original test of Queckenstedt. These include: instantaneous touch compression, introduction of the time element, study of the manner of the rise and fall and pressure index. Therefore the term lumbar manometric test is preferred to Queckenstedt test.

3. The more delicate variations of the manometric test are best seen when charted graphically.

4. The complete manometric chart should include three phases: phase A, the response to instantaneous touch compression; phase B, the rise and fall on deep compression; phase C, the change in pressure level after withdrawal of 7 cc. of fluid.

5. Instantaneous touch compression affords essentially the same information as that deduced after deep compression. It is more delicate than deep compression, for it does not produce defense mechanisms such as reflex coughing and straining. These may vitiate the response to deep compression.

6. The response to deep compression in the positive manometric tests can be subdivided into three groups: (a) absolute blocks with no rise on deep compression; (b) complete block with slight rise on deep compression; (c) blocks with delayed rise, delayed fall or rise with establishment of a new high level.

7. The pressure index is the ratio of the new level after the removal of 7 cc. of fluid and the original pressure level. This has been termed the third phase, and is considered one of the most important parts of the manometric test.

8. Technical details must be watched minutely. If the head is in the wrong position or if the patient is not relaxed, false initial pressure will be obtained. Arachnoid or a nerve root against the needle, may cause an apparent block. When a block is obtained, the needle should be rotated, and the patient told to strain in order to make sure that the apparatus is patent.

9. The balance of the cerebrospinal fluid pressure in the subarachnoid space is so delicate that some variations in its pressure cannot be determined unless a spinal fluid manometer is used. These variations may not be appreciated if the air manometer of Claude or the mercury manometer is used.

10. The lumber manometric test demonstrates an obstruction of the subarachnoid space. The level of the obstruction should be determined by the neurologic examination and not by mechanistic measures. When the neurologic examination does not permit determination of a level, then and then only is iodized oil indicated. Since both iodized oil and cerebrospinal fluid can pass an incomplete obstruction, iodized oil is of no greater aid than the manometric test to determine incomplete blocks.

11. In postoperative cases in which improvement has not been as rapid or as complete as expected, a second lumbar manometric test should be performed as a routine to prove the patency of the subarachnoid space.

12. The total protein content of the spinal fluid is of great value as additional evidence, especially when the manometric test is equivocal. The total protein content was below 40 mg. in 88 per cent of the negative charts and well above 40 mg. in 78 per cent of the positive charts.

13. In compression of the spinal cord, the increase in the protein content is produced by diapedesis accompanying venous stasis, irrespective of the nature of the compression. It is present whether the compression is caused by an intradural or extradural tumor or by fracture dislocation of the vertebrae with compression.

14. In adhesive arachnoiditis, subarachnoid block may be complete without an increase in the total protein content. This is rather to be expected, since subarachnoid block in this disease may be complete without venous stasis, and consequently diapedesis does not occur.

15. The globulin excess in the spinal fluid followed closely the increased total protein. Excess of globulin was found in only 1 per cent of the negative charts as compared with 61 per cent of the positive charts.

16. Xanthrochromia was obtained far less often than either a globulin excess or a protein increase. Xanthrochromia occurs when there is venous stasis of long duration.

CIRCUMSCRIBED SUPPURATIVE (NONTUBERCULOUS) PERIPACHYMENINGITIS

HISTOPATHOLOGIC STUDY OF A CASE *

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The term "peripachymeningitis" was given by Traube [1] to a combined inflammation of the spinal meninges (dura and pia-arachnoid) and the epidural connective tissue situated between the dura and the periosteum of the vertebrae. Albers [2] termed this condition perimeningitis; Braun [3] called it epimeningitis; others called it pachymeningitis spinalis externa. As the foregoing terms imply an inflammation only of the epidural or epimeningeal tissues, it would be proper to reserve Traube's term peripachymeningitis for cases in which a perimeningitis is associated with a pachymeningitis and leptomeningitis. In either condition the main pathologic changes are in the perimeningeal tissues which, as first pointed out by Vulpian,[4] may be either infiltrated with pus or transformed into "sclerotic tissue." This is sometimes so abundant that it may resemble a veritable new growth. It is thus a purely local process involving only a circumscribed area in the epidural space. As a rule, however, the epidural lesions are diffuse, the dura being encircled by and bathed in pus, sometimes throughout its entire length. In the cases of Spencer,[5] Morawitz,[6] and Schmalz,[7] for instance, the pus extended from the cer-

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* From the Pathologic Laboratories of the State Psychopathic Institute and the Research and Educational Hospitals of the University of Illinois.

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5. Spencer, W. H.: Case of Idiopathic Inflammation of the Spinal Dura Mater, Lancet **1**:836 (June 14) 1879.

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7. Schmalz, A.: Ueber akute Pachymeningitis spinalis externa, Virchows Arch. f. path. Anat. **257**:520, 1925.

vical to the lumbar region; in the case of Hinz,[8] from the fourth cervical to the eighth thoracic vertebra and in that of Humbert and Perret,[9] it reached from the third cervical vertebra to the sacrum. Rare as diffuse epidural suppurations generally are, they are much more common than the circumscribed variety, in which the suppuration is represented by minute abscesses enclosed within a mass of granulation tissue. Such cases have been recorded by Mannkopff,[10] Folly,[11] Fuchs,[12] Runge,[13] Henneberg,[14] Schmalz [7] and Dandy.[15] An additional case is here recorded with a more or less complete outline of the pathologic features and their probable significance.

REPORT OF CASE

Clinical History.—A white girl, aged 21, first consulted Dr. W. W. Hartman, on Dec. 30, 1925, for furuncles of the face, neck and buttocks of one year's duration. At the age of 4, the patient suffered from bilateral otitis media and frequent attacks of tonsillitis, for which she had had two tonsillectomies. On examination, Dr. Hartman found a somewhat thickened membrana tympani, furuncles on the face and back of the neck and numerous scars from old furuncles on the buttocks. The urine did not contain any sugar or albumin; the specific gravity was 1,020. Examination of the blood revealed 84 mg. of sugar per hundred cubic centimeters. Cultures from the furuncles showed predominance of *Staphylococcus aureus.* Autogenous vaccine treatment rendered the patient free from furuncles for a "period of one month." The patient's mother, however, said the patient had not had furuncles for a period of about four months, during which time the patient enjoyed good health and was able to make an automobile trip to New York. In August, 1926, she again began to have "boils"—one appeared on the chest, two around the rectum, and on August 19, one developed in the lower thoracic region of the back, about 1 inch to the left of the spine. On August 22, she assisted, for a period of forty-five minutes without stopping, in administering artificial respiration to a girl who drowned and she "thought she sprained her back" since she experienced a sharp pain in that region. She said that there was a spot in the spine, which when touched produced a peculiar sensation that extended down the legs. About four days (August 26) after the physical exertion, the patient

8. Hinz: Ueber einen Fall von Perimeningitis spinalis, Deutsche med. Wchnschr. **47**:1229, 1921.

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14. Henneberg: Pachymeningitis externa purulenta nach Nackenabscess, Zentralbl. f. d. ges. Neurol. u. Psychiat. **25**:96, 1921.

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complained of severe pain in the back and chest, and on September 1, that is, five days afterward, she felt numbness in the lower extremities and had difficulty in moving them. The same night she found herself paralyzed and unable to void urine or move the bowels.

Dr. Ludwig Loeb found a complete paraplegia of the lower extremities, bilateral Babinski phenomenon and complete anesthesia up to the level of the twelfth thoracic segment, rectal and urinary retention, and pain over the middle portion of the spine. The breathing was at times dyspneic, but the temperature was

Fig. 1.—The epidural space between the bone and the posterolateral surface of the spinal cord is filled with a granulation mass; the epidural fat tissue (*E*) adjacent to the lamina of the vertebra is well retained; the spinal cord is of normal configuration and surrounded by a wide subarachnoid space; signs of mechanical cord compression are absent; the white columns show areas of rarefication "*L*" ("Lücken" formation): in the epidural masses three small abscesses (*AAA*) are distinct, but better shown in figure 2; *D*, dura; *RR*, spinal roots. Van Gieson, × 4.

normal and vasomotor and trophic disturbances were absent. I confirmed these observations (September 3) and interpreted them as manifestations of an extradural compression of the spinal cord; immediate operation was advised and consented to.

Two days later, as the records of the Michael Reese Hospital showed, the clinical picture was somewhat different: the knee and ankle reflexes had disappeared, the anesthesia reached the inguinal region and was covered by a zone of hyperesthesia up to the umbilicus. Spinal puncture yielded a clear sterile fluid that contained 1 plus globulin and 32 lymphocytes per cubic millimeter, and gave negative Wassermann and colloidal gold tests. Examination of the blood revealed: hemoglobin, 75 per cent; red cells, 5,020,000 and white cells, 14,600, of which 70 per cent were neutrophil, 14 per cent small mononuclear, 14 per cent large mononuclear and 2 per cent transitional.

The general condition during the following two days as well as the temperature and pulse rate were normal, but the breathing was often labored. On the

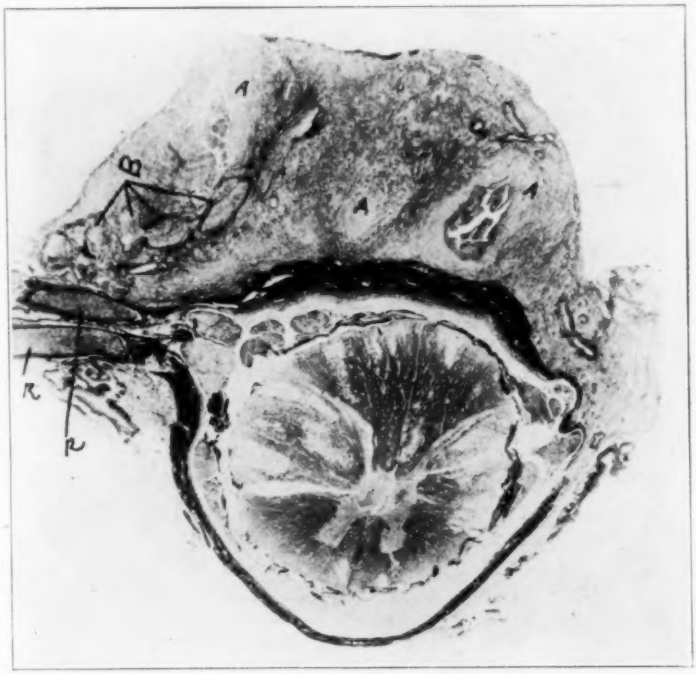

Fig. 2.—Spinal cord, normal in shape, surrounded by a thickened dura and patent subarachnoid space; the foci of rarefication in the spinal cord and the abscesses in the epidural mass (*AAA*) are distinct; at *B*, several foci well encapsulated; the blending of the epidural mass and the dura is well shown. Van Gieson; × 5.

morning of September 7, the date set for the operation, the patient complained of "being distended" and of a "desire to void." The nurse was about to catheterize the patient and in so doing moved the legs. Almost immediately the patient became pulseless, developed Cheyne-Stokes respiration, foamed at the mouth and died within fifteen minutes.

Necropsy.—The examination was confined to the spinal cord and a small portion of the vertebral column. The latter appeared normal; between the periosteum of the eighth and ninth thoracic vertebrae and the posterolateral surface of the

dura a thick mass of granulation tissue was present (fig. 1) enclosing three small abscesses (fig. 2); from these *Staphylococcus aureus* was isolated. The mass was loosely attached to the periosteum of the arches and was adherent to the dura. The spinal cord was of normal shape (fig. 2) and only in places of improper handling exhibited defects in the form of cavities. The dura was thickened at the levels covered by the epidural mass, and was not adherent to the pia-arachnoid.

The bones, epidural tissues, meninges, the roots and the spinal cord at its various levels were studied microscopically.

Fig. 3.—Higher magnification of one of the abscesses shown in figure 2; it is bordered by a dense rim of cells (at *R*) and encircled by a young connective tissue layer (light ring outside). Van Gieson; × 24.

Microscopic Examination.—The epidural mass, as figure 2 shows, contained three distinct abscesses (*A, A, A*) in the form of dense foci of cell bodies. Some of these were plasma cells, or lymphocytes; the majority were polymorphonuclear cells, many of which were enclosed within macrophages. The latter were numerous at the periphery of the abscess where, in addition, many fibroblasts were present. The foregoing types of cell bodies—fibroblasts, macrophages, lymphocytes, plasma cells and polymorphonuclear cells—formed a thick or dense rim (fig. 3) around the abscess, an embryonic capsule as it were.

Bordering on the latter was a distinct connective tissue layer, unusually vascular and consisting mainly of fibroblasts and a few polymorphonuclear cells. In

some parts of the wall of the abscess, the blood vessels were numerous, distended, hyperemic and infiltrated, their adventitial and endothelial cells proliferated and causing, in some instances, obliteration of the lumen.

Aside from these three purulent foci with rather ill defined, incompletely formed capsules, there were other foci that possessed a connective tissue membrane much better developed (fig. 2 *B*). The contents of such foci were polyblasts or large lymphocytes, many of which showed mitotic figures. Plasma cells were exceptional here, while polymorphonuclear cells and macrophages were entirely absent. Such well encapsulated foci, with no polymorphonuclear cells, may be looked on as areas in which an abscess formation was checked by a timely

Fig. 4.—Dural and epidural infiltrations at the twelfth thoracic segment. They involved the trabeculae of the epidural fat, without abscess formation; below is the subarachnoid (appearing in the photograph as a subdural space because of the collapsed arachnoid) space and an infiltrated pia-arachnoid; *BV*, infiltrated pial blood vessel. Van Gieson; × 60.

connective tissue proliferation. The remaining portions of the microscopic field were crowded with numerous foci of lymphocytes, plasma cells and mast cells. Such foci were irregularly invaded and traversed by rows of numerous fibroblasts and collagen connective tissue fibers. Like the areas harboring the abscesses they contained many blood vessels, the majority of which were patent. A few were obliterated by the proliferated intima, while the adventitia was always hyperplastic forming dense rings of connective tissue infiltrated with various hematogenous

cells. The origin of some of the rings traversing and separating the foci could be traced to the hyperplastic adventitia, some to the subjacent dura, and some to the fibroblasts or their progenitors, polyblasts. The microscopic field appeared, therefore, in specimens stained with the method of van Gieson, to consist of granulation tissue and connective tissue strands that seemed to break up the former into numerous small foci, some of which, as pointed out, were abscesses.

The changes outlined were present throughout the entire thickness of the epidural mass, being somewhat less in evidence near the bone and the dura. In the former, that is to say in the areas bordering on the periosteum of the vertebrae, the epidural fat was well retained (fig. 1), though markedly infiltrated with

Fig. 5.—Dura is infiltrated, the infiltration cells filling the intradural spaces and reaching its inner layer which is markedly infiltrated. *Ar.*, arachnoid membrane covering a portion of the posterior roots; *P*, infiltrated perineurium, reproduced under higher power in figure 8. Toluidine blue; × 35.

polyblasts and lymphocytes, without any abscess formation or proliferation of connective tissue elements. Equally mild were the inflammatory phenomena in the neighborhood of the dura, where the infiltrating cells were much more numerous, including among others plasma cells with mitotic figures, fibroblasts and mast cells.

The infiltration did not spare the dura itself. This membrane generally formed a barrier (fig. 2) against a further extension of the inflammatory process, for in many places it was directly invaded by the foregoing inflammatory elements. It

appeared in such places thickened and blended with the epidural mass. The interspaces of the dura were markedly infiltrated mainly with plasma cells and polyblasts which formed cell foci gathered around hyperemic veins.

Even above and below the levels of the epidural mass the dura contained such foci for a short distance, though much smaller and less compact (fig. 4). Around the posterior, and less so around the anterior, roots the dural infiltrations exhibited numerous mast cells scattered among plasma cells and fibroblasts.

Not only the epidural and intradural spaces, but also the inner surface of the dura showed marked signs of inflammation. As figure 5 shows, the inner layer

Fig. 6.—Perineural infiltration of a posterior root (masses of light fibers in the center); the dark masses enveloping the root fibers are the epidural infiltrations invading and obliterating the perineural spaces; the cellular infiltrations are especially well seen at the lower end of the root fibers and reproduced under higher power in figure 7. Toluidine blue; × 80.

of the dural membrane was thickly infiltrated with hematogenous elements, principally around the posterior roots where (fig. 6) it blended with the arachnoid membrane forming one impenetrable mass. The subdural space was otherwise, that is to say around the spinal cord, patent, in marked contrast to the epidural space which at the level of the last four thoracic segments was entirely obliterated

by a mass of granulation tissue. Above the ninth and below the twelfth segments the epidural infiltrations were absent. Here only the epidural tissue exhibited, for a short distance, mild infiltration with lymphocytes and plasma cells, while in the upper dorsal or lumbosacral areas epidural infiltrations were entirely absent.

The arachnoid membrane was loosely attached to the dura and to the roots in their course within the subarachnoid space. Only in their preganglionic portion, where the posterior and anterior roots meet to form the so-called radicular nerve of Nageotte, was the arachnoid membrane blended above with the dura and below with the roots, thus obliterating both the epidural and the subarachnoid spaces (fig. 6). The perineural sheaths of the roots showed here marked pro-

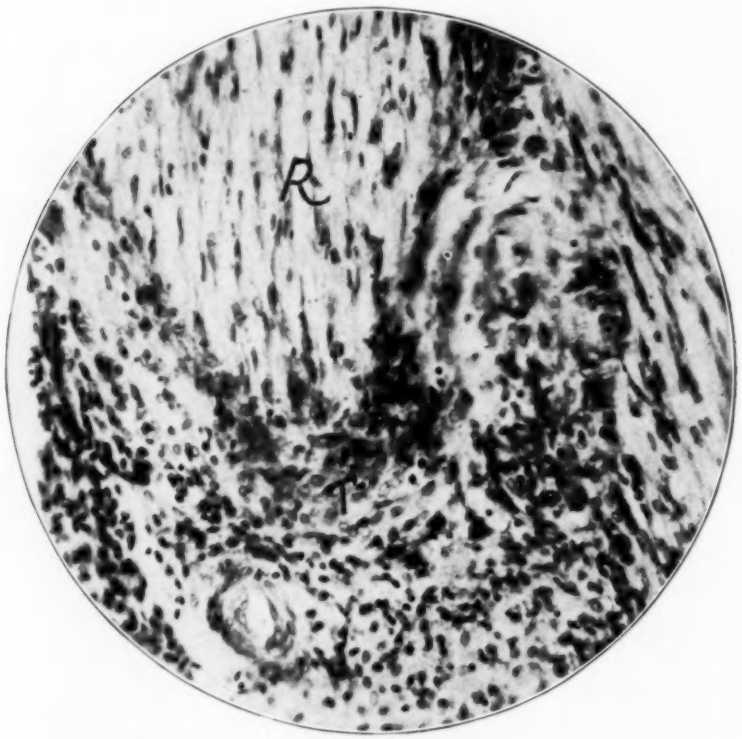

Fig. 7.—Proliferation of the mesothelial cells of a posterior root; the latter is triangular in shape, occupying the upper two-thirds (*R*) of the picture; the lower portion of the picture and around the apex of the triangle, at *T* for instance, numerous mesothelial and other cells mentioned in text. Toluidine blue; × 200.

liferation of the mesothelial cells (fig. 7); often they were infiltrated with hematogenous elements, such as lymphocytes (fig. 8), polyblasts and a great many mast cells. The roots thus showed a perineuritis, seldom an endoneuritis, while their nerve fibers appeared generally well retained. The foregoing changes were present in both posterior and anterior roots, but were much more marked in the former.

The pia also was more or less involved—it showed infiltrations (fig. 4) which extended along the intraspinal prolongations, the ligamenta denticulata and the adventitial spaces of the blood vessels, which were also distended and hyperemic.

Adhesions were not present between the pia and arachnoid; the subarachnoid space therefore was patent, encircling the cord as a wide empty ring (fig. 2). The cord, as the same figure shows, preserved its shape and configuration, did not exhibit any signs of mechanical compression, and its gray and white substances were well defined. The white substance, however, exhibited changes, mainly in the form of rarefication (fig. 2) scattered over the various spinal cord columns, especially the posterolateral. In the posterior columns they were often confined to the root entrance zone of Westphal, but were also present in the columns of Goll. The foci showed as "Lücken," that is, as a network of numerous more or less distended spaces (fig. 9) of various sizes and shapes. Their walls were of

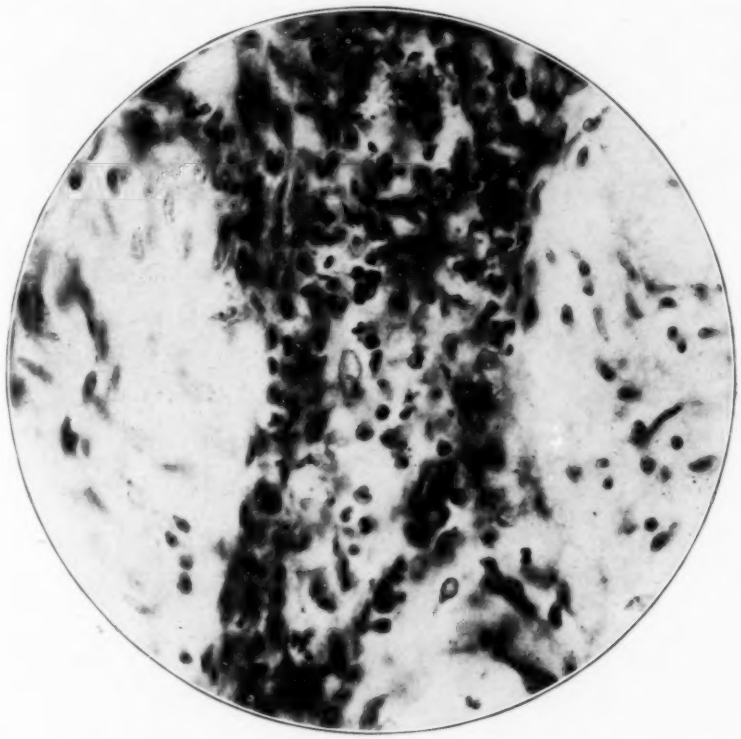

Fig. 8.—Infiltration of the perineurium of the posterior roots with hematogenous elements described in text. A higher magnification of *P* in figure 5. Toluidine blue; × 420.

thickened glia covered with numerous glia nuclei rich in chromatin. The contents of some "Lücken," which were usually empty, were homogeneous masses, round or oval, and much resembled amyloid bodies (fig. 9). However, they did not give the iodine or other reactions for amyloid. Some such bodies contained a somewhat dark center, also homogeneous, evidently a changed axon. The contents of the dilated spaces were crosswise connected with the surrounding glia rings by small bands, while in other instances the glia rings invested the contents closely, or were torn, causing the formation of small cavities filled with broken

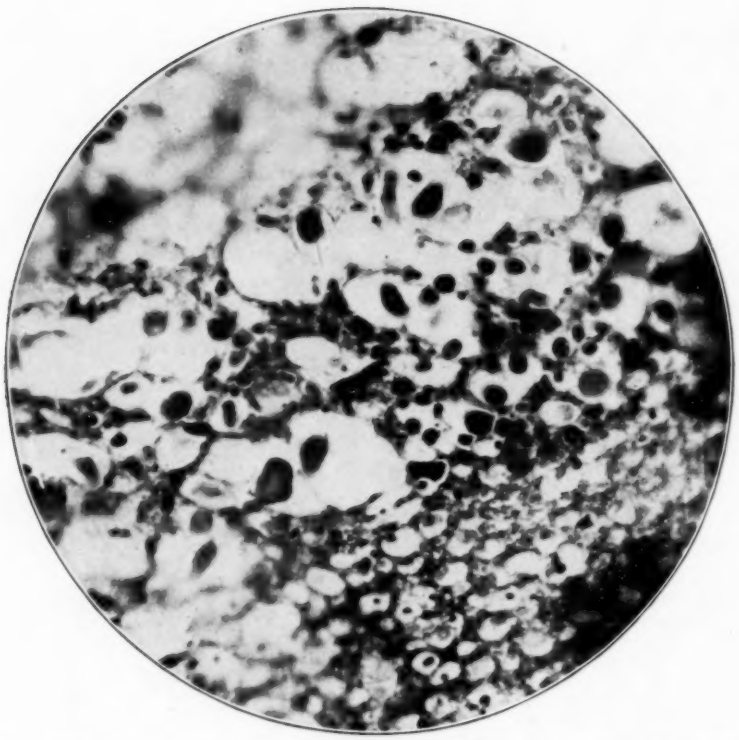

Fig. 9.—Areas of rarefication ("Lücken" formation), from the posterior columns; the contents of the enlarged spaces bordered by thickened glia are broken up axons and myelin, resembling amyloid bodies. Uranin gallein; × 290.

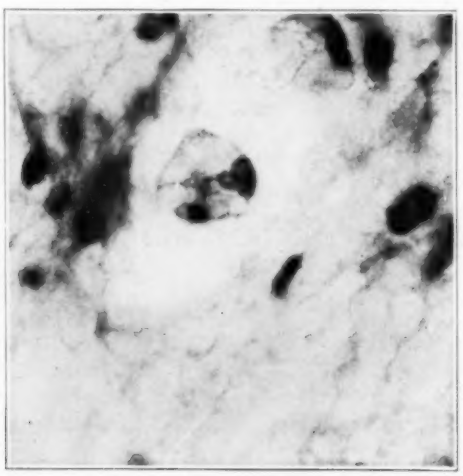

Fig. 10.—Myelophages and other reactive phenomena in the rarefied area; described in text. Toluidine blue; × 600.

up glia or fragments of axons and myelin. In the tissues adjacent to and within the foci of rarefication were numerous myelophages (fig. 10), cytoplasmic glia cells and scattered nuclei unusually rich in chromatin. The latter two varieties of cell forms were also more or less in evidence in the normal portions of the white columns. Ameboid glia, so-called "Füll-körperchen," granular gitter cells, were not found anywhere. No phenomena of ascending or descending degeneration were present, but the blood vessels were abundant, their advential walls thickened. Longitudinal sections from the rarefied areas showed practically the same changes and therefore do not need any special description.

The foci of rarefication were found only in the white substance, at the levels of from the ninth to the twelfth thoracic segment where the epidural thickening

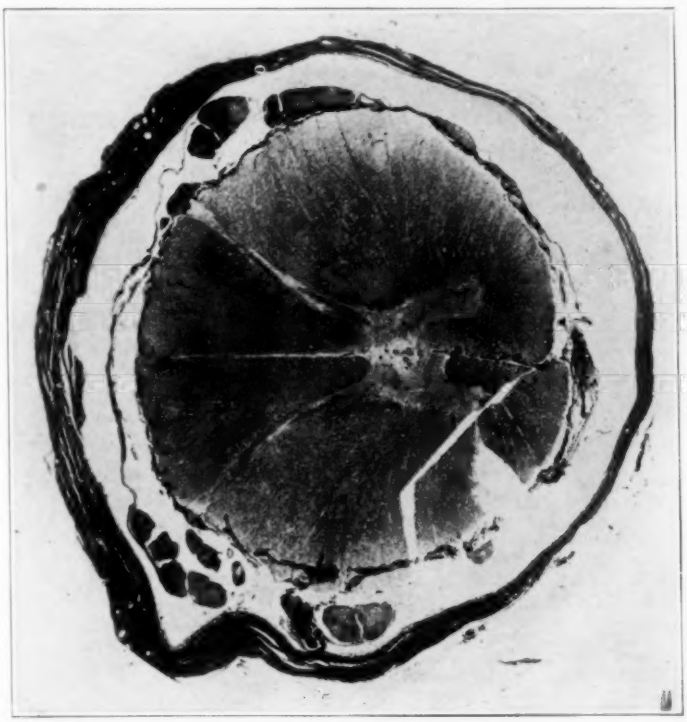

Fig. 11.—Thoracic cord above the infiltrated epidural space; absence of cord changes such as "Lücken" formation; the dura is thickened over the posterolateral surface of the spinal cord. Weigert-Pal counterstained with Van Gieson; × 8.

was situated. Above and below these levels the spinal cord was normal (fig. 11); it showed no foci of rarefication nor vascular changes. The former, as noted, were also absent in the gray matter, the anterior as well as the posterior horns, throughout the spinal cord. However, it was excessively crowded with large cytoplasmic glia, glia nuclei and, in exceptional instances, the blood vessels of the anterior horns of the gray matter showed perivascular infiltrations (fig. 12) with lymphocytes, polyblasts and some polymorphonuclear cells. Blood vessels were, in general, numerous around the central canal, which was either dilated, elongated or broken up, that is, devoid in some places of ependymal cells. These were,

especially in areas with the epidural thickening, proliferated, forming several layers (fig. 12). The contents of the central canal were either a homogeneous substance containing lymphocytes or hematogenous elements only.

The ganglion cells were well preserved. Sometimes they showed mild chromatolysis, slight swelling or phenomena of axonal reaction, satellitosis and neuronophagia.

The laminae of the eighth vertebra were decalcified with nitric acid and did not reveal any macroscopic or microscopic changes.

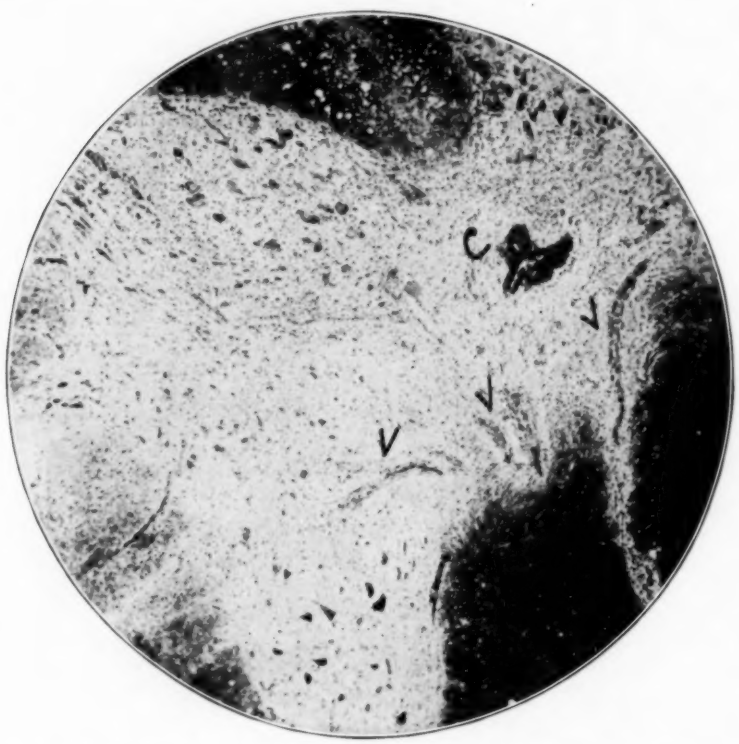

Fig. 12.—Vascular infiltration (*VVV*) of the anterior horns; the central canal (*C*) shows marked ependymal proliferation. Toluidine blue; × 35.

SUMMARY OF PATHOLOGIC OBSERVATIONS

Obliteration of the posterior epidural space, at the level of the ninth to the twelfth thoracic segments, by a granulation mass harboring three small abscesses, incompletely encapsulated; extensive dural nonpurulent infiltrations; perineuritis of the ganglionic portion of the spinal nerve roots, especially the posterior; patent subarachnoid space; nonpurulent leptomeningitis; scattered inflammation of the anterior horns of the gray matter; absence of inflammatory phenomena and presence instead of foci of liquefaction in the white substance of the spinal cord, especially in the posterolateral columns, corresponding with the levels of the epidural

mass; absence of secondary degeneration and of bone changes such as osteitis, osteomyelitis or periostitis, and absence of any changes above and below the areas occupied by the granulation tissues and of visible signs of compression of the cord were noted.

COMMENT

The symptoms generally may be defined as marked inflammation of the perimeningeal tissues and the meninges themselves (peripachymeningitis), and scattered degeneration of the white columns of the spinal cord, both types of changes confined to the lower thoracic region. Of these, the epidural changes—the granulation tissue enclosing abscesses—undoubtedly were the primary; the dural, pia-arachnoid, perineural root and spinal cord changes were secondary. The changes in the cord were responsible for the clinical picture of transverse myelitis and much resembled those described by Kahler,[16] Schmaus,[17] Rosenbach and Schtsherback,[18] Heymann,[19] Bornstein,[20] and others in experimental so-called pressure myelitis. This was produced by introducing, between the dura and the vertebral arches, beeswax, silver rods, laminaria or similar more or less hard objects; in this case, it was produced by the presence in the same location of thick granulation tissue. The similarity between the experimental changes and those in this case was in their localization, the character of the parenchymatous changes of the cord and in the fact that they were not diffuse, but circumscribed, that is to say confined to a few segments of the spinal cord, leaving the rest intact. Thus, as in the experiments, the changes in this case were in the posterior epidural space, mainly around the posterior columns, though, as noted, they extended at some levels over the lateral columns.

Such a localization was also present in all the clinical cases of peripachymeningitis recorded. The explanation given for such a preferred if not exclusive localization is that the epidural space is better developed posteriorly to the dura, especially in the midthoracic region (Dandy [15]). The ventral epidural space, though present, is much less in evidence; it is rather a capillary or probably a potential space. Because of the too close contact of the dura to the dorsal longitudinal ligament it lacks here the

16. Kahler, O.: Ueber die Veränderungen, welche sich im Rückenmarke in Folge einer geringradigen Compression entwickeln, Ztschr. f. Heilk. **3**:187, 1882.

17. Schmaus, H.: Quellungzustände, Lubarsch-Oestertag's Ergebn. d. allg. Pathol. u. path. Anat. **13**:711, 1894.

18. Rosenbach, P., and Schtsherback, A.: Ueber die Gewebsveränderungen des Rückenmarks in Folge von Compression, Virchows Arch. f. path. Anat. **122**:56, 1890.

19. Heymann, B.: Beitrage zur pathologischen Anatomie der Rückenmarkscompression, Virchows Arch. f. path. Anat. **149**:526, 1897.

20. Bornstein, M.: Experimentelle und pathologisch-anatomische Untersuchungen über die Kompression des Rückenmarks, Ztschr. f. d. ges. Neurol. u. Psychiat. **31**:184, 1916.

epidural fat and the connective tissue which is often so abundant in the posterior epidural space. Yet, in the case of Mills and Spiller,[21] the ventral epidural space was implicated, while the dorsal "presented nothing abnormal." In the spinal cord they found degeneration of the columns of Goll in the cervical region; of the spinocerebellar tracts; of the peripheral portions of the cord; of the pyramidal tract (in the lumbar region), and a partial degeneration of the posterior columns; the roots were normal; there was no pachymeningitis or leptomeningitis. The extensive degeneration found by them in the thoracic region, they stated, was hard to explain.

In the case here recorded the relations were different. The ventral aspect of the dura was normal, but its dorsal surface was covered by a mass of young connective tissue; in addition there was a pachymeningitis and a leptomeningitis; the roots were affected by a perineuritis; signs of secondary degeneration were absent or showed as mild glia reaction. The changes in the spinal cord, similar to those in the experimental myelitis from pressure (swollen axons and myelin, broken up myelin, distention of the glia tissue spaces, thickening of the glia septums and hyperplasia of the vessel walls), were as in the latter present only in the white substance at the levels that corresponded with the maximum of the epidural infiltrations. The changes in the gray matter were altogether insignificant and greatly overshadowed by those of the white substance, which, as said, were alone responsible for the clinical picture.

The cause of the parenchymal changes was looked for by the experimenters in "lymph stasis" (Kahler[16]), that is to say, in the stagnation of the tissue fluids of the spinal cord. Kahler assumed that the discharge or flow of the "lymph" from the adventitial spaces of the spinal cord into the subarachnoid space was obstructed by the epidural pressure on the cord. On the other hand, Schmaus[22] pointed out that in some cases the peridural changes and the resulting obstruction of the "lymph spaces" or of the blood vessels were not sufficient to cause stasis; that there are additional factors, such as obstruction of the dural venous plexuses, irritative and mainly inflammatory phenomena. The result of all these factors is "stagnation edema" which causes distention of the tissue spaces, their filling up with "lymph" in which the nerve fibers are bathed. Excessive "lymph" accumulation around nerve fibers was shown by Rumpf[23] to affect their vitality and cause breaking up of the myelin,

21. Mills, Charles K., and Spiller, W. G.: Case of External Spinal Pachymeningitis Implicating the Entire Ventral Space of the Spinal Dura, Brain **25**:302, 1902.

22. Schmaus, H.: Vorlesungen über die pathologische Anatomie des Rückenmarks, Wiesbaden, J. F. Bergmann, 1901.

23. Rumpf, T.: Ueber die Einwirkung der Lymphe auf die Centralorgane, Pflüger's Arch. f. d. ges. Physiol. **26**:415, 1881.

axon and their final dissolution, with formation of areas of liquefaction and other changes already described. The changes in the spinal cord as found in the experimental work were thus due not to direct pressure, but to the disturbed "lymph" or blood circulation in the meninges.

In the case described here the relationship between the cord and the meningeal changes is much clearer. As pointed out, the epidural inflammation here was combined not only with that of the dura itself, but also with that of the denticulate ligaments, pia-arachnoid membrane and, what is still more important, with that of the perineural spaces of the spinal roots. This denotes that substances from the epidural space, under certain conditions, such as excessive peridural infiltrations, may reach the intradural channels and the perineural spaces of the spinal roots. The latter, as Key and Retzius [24] demonstrated by their injection experiments, are continuations of the subdural and subarachnoid spaces. They are evidently the principal avenues of escape of the cerebrospinal fluid from the subarachnoid space and indirectly of the tissue fluids of the cord itself. Under normal conditions the tissue fluids of the spinal cord are drained by the subarachnoid space and probably by the central canal; from the former the contents are discharged by way of the perineural root spaces into the spinal ganglia and the peripheral nerves (Key and Retzius [25]). Under the pathologic conditions that existed in my case (an obstruction of the epidural space by an inflammatory mass), the perineural spaces of the roots were also obstructed by the same mass (fig. 6). This resulted in the stoppage of draining of the subarachnoid and cord tissue fluids with the consequent accumulation of the latter in the parenchyma of the spinal cord and destruction of its nerve fibers.

Whether such a phenomenon, obstruction of the perineural root spaces, also occurred in the experimental cord compression, I am unable to tell, for the condition of the roots and their spaces is not mentioned by the experimental workers. Yet it is of paramount importance and significance, for in areas above and below the epidural infiltrations such an obstruction was absent, and consequently the draining of the cord tissue fluids was unhampered; parenchymal changes, such as liquefaction of the white substance, therefore, were not present. Absence of such phenomena throughout the gray matter was most likely due to the fact that the draining of the latter is done not by the subarachnoid space but by the central canal.

One more fact of pathologic interest should be noted—the epidural lesion was circumscribed, that is to say confined to a few segments. As noted, this is a rare occurrence, for suppurative epidural lesions are

24. Key, A., and Retzius, G.: Studien in der Anatomie des Nervensystems, Arch. f. mikr. Anat. **9**:308, 1873.

25. Key, A., and Retzius, G.: Stud. d. Anat. d. Nervensystems und des Bindegewebes, Stockholm, 1876, vol. 2, p. 111.

usually diffuse. The probable reason for suppurative lesions becoming in some instances localized may lie in the extent of the reactive phenomena, which in this case were intensive as evidenced by a fair though incomplete capsule formation around the abscesses. The incompleteness of the capsule, the early signs of secondary degeneration, such as the presence of myelophages and cytoplasmic glia, also denote that the process was young, not more than two weeks old. This corresponds exactly with the clinical facts, the time of the onset of the symptoms after a trauma, a "sprain" of the back about fifteen days preceding the patient's death. The trauma, "sprain" or rather strain to the back undoubtedly played some rôle in the causation of the disease, as it was also present in the cases of Lewitzky,[26] Lemoine and Lannois,[27] Hunt,[28] Kaminski [29] and Runge.[13] However, this etiologic factor is of secondary importance; the primary factor unquestionably was a hematogenous staphylococcus infection from an extensive furunculosis. This has been mentioned in a number of cases as the principal etiologic factor of diffuse and circumscribed epidural suppurations (Schönwerth,[30] Hoestermann,[31] Kaminski,[29] Morawitz,[6] Fuchs,[12] Henneberg,[14] Braun,[3] Cassirer,[32] Pulvirenti,[33] Spiller and Wright,[34] Schwab,[35] Dandy,[15] Schmalz [7]), though any other source of hematogenous infection may be the cause, such as nasal (Keienberg [36]), bronchial (Schick [37]), tonsillar (Folly [11]),

26. Lewitsky, P.: Ein Fall von Peripachymeningitis spinalis, Berl. klin. Wchnschr. **14**:227, 1877.

27. Lemoine, G., and Lannois, M.: Périméningite spinale aiguë, Rev. de méd. **2**:533, 1882.

28. Hunt, J. R.: Acute Infectious Osteomyelitis of the Spine and Acute Suppurative Perimeningitis, M. Rec. **65**:641, 1904.

29. Kaminski, R.: Eine metastatische Perirachymeningitis und Periostitis spinalis purulenta nach Furunculose, Diss., Greifswald, 1917; abstr., Ztschr. f. d. ges. Neurol. u. Psychiat., Ref. **15**:249, 1918.

30. Schönwerth, A.: Ueber einen Fall von akuter Wirbelosteomyelitis, München. med. Wchnschr. **49**:269, 1902.

31. Hoestermann: Ueber Myelitis transversa, Neurol. Centralbl. **32**:1007, 1913.

32. Cassirer, R., in Oppenheim: Lehrbuch der Nervenkrankheiten, ed. 7, Berlin, S. Karger, 1923, vol. 1, p. 419.

33. Pulvirenti, S.: Sopra un caso di spondilite acute purulenta lombare, Policlinico **28**:27, 1921.

34. Spiller, W. G., and Wright, V. W. M.: Extradural Abscess of the Midthoracic Region of the Spinal Canal Secondary to a Boil in the Neck, Arch. Neurol. & Psychiat. **5**:107 (Jan.) 1921.

35. Schwab, E.: Akute eitrige Perimeningitis, Deutsche med. Wchnschr. **50**: 1544 (Nov.) 1924.

36. Keienburg, F.: Ueber akute eitrige Perimeningitis, Med. Klin. **20**:640 (May) 1924.

37. Schick, K.: Pachymeningitis spinalis externa purulenta als Metastase nach Diplokokken bronchitis, Wien. klin. Wchnschr. **22**:1185 (Aug. 26) 1909.

phlebitis (Oppenheim [38]), and others. A few cases have been recorded in which no cause could be detected (Spencer,[5] Humbert-Perret,[9] Deléarde,[39] Taylor and Kennedy [40]), and called by some idiopathic or primary. As R. Hunt [28] pointed out, primary suppurative epidural lesions do not exist, but are, he believes, identical with acute osteomyelitis of the spine.

Whatever the origin of the epidural suppurations, the fact remains that they may cause degenerative conditions of the white substance of the spinal cord. In fact, these may result from any epidural lesion, even nonsuppurative such as syphilis, tumors, and lesions of the bone; what is still more remarkable is that under certain conditions, they may result in changes of the spinal cord typical of tabes dorsalis.

It is needless to point out that when recognized early and in the absence of sudden complications such as occurred in this case (pulmonary emboli) surgical treatment may result in cure (cases of R. Hunt,[28] Ryerson,[41] Taylor and Kennedy,[40] Pulvirenti,[33] Dandy [15]).

CONCLUSIONS

1. A hematogenous infection from an extensive furunculosis of old standing caused a severe noninflammatory lesion of the spinal cord with a clinical picture of so-called transverse myelitis.

2. The infection resulted in the formation of epidural abscesses and an extensive reactive peripachymeningitis.

3. An intermediary involvement of the vertebrae in the form of periostitis or osteomyelitis in this type of epidural infection is not obligatory.

4. The meningeal lesions may extend over the perineurium of the spinal roots and cause stasis of the tissue fluids in the spinal cord and its secondary degeneration.

5. The changes are similar to those found in so-called pressure myelitis produced experimentally.

ABSTRACT OF DISCUSSION

Dr. James B. Ayer, Boston: I have two cases in mind which bear on this subject. The first is that of a young man whom I saw in 1923. He had rapidly developed symptoms of transverse myelitis over a period of two weeks. On looking

38. Oppenheim, E. A.: Ueber einen Fall von extraduraler Spinaleiterung, Berl. klin. Wchnschr. **47**:1412, 1910.

39. Deléarde, A.: De la périméningite aiguë spinale, Gaz. hebd. de méd. **47**: 493 (May 27) 1900.

40. Taylor, A., and Kennedy, F.: A Case of Extrathecal Abscess of the Spinal Cord, J. Nerv. & Ment. Dis. **57**:484, 1923.

41. Ryerson, E. W.: Spastic Paraplegia Due to Infectious Granuloma on the Dura. Operation, Recovery, Arch. Neurol. & Psychiat. **7**:270 (Feb.) 1922.

for a cause I found a furuncle in the upper part of the back, somewhat above the level indicated by the neurologic examination. He had complete spinal subarachnoid block on lumbar puncture, and I advised immediate decompression for epidural abscess. He was operated on within twenty-four hours of the development of (nearly) complete transverse symptoms. He recovered sufficiently to walk with assistance, but three years later he was still in a hospital for chronic patients. The epidural abscess was said to have been localized; unfortunately, cultures were unsatisfactory. Here, then, is a patient who was operated on as quickly as I think would be likely in any case; drainage was established, and yet he is paralyzed. This result would seem to be adequately explained by the conditions in the spinal cord as shown in Dr. Hassin's case.

The picture which Dr. Hassin showed of a markedly degenerated cord at the level of compression was duplicated in the report of a case which Dr. Viets and I published in 1916.[42] A carpenter had scratched his breast with a nail, with the subsequent development of a local abscess, which in due course healed. Some weeks later symptoms appeared which culminated in paraplegia and "transverse myelitis." At autopsy we found that there was a diffuse epidural abscess showing *Staphylococcus albus*. The cord was disintegrated at the site of compression, simulating the picture Dr. Hassin has shown.

Dr. Hassin did not stress one important point. In spite of the fact that these epidural abscesses may be present for days and even weeks, subdural and subarachnoid infection does not readily occur. In our first case meningeal infection did not occur, and in our second case there was no evidence of subdural infection although the pus must have overlain the dura for at least nine days. A case reported by Oppenheim gave no subdural infection after twenty-five days!

Dr. Walter Freeman, Washington: The diagnosis of extradural abscess is always astounding and a good many of the surgeons will question it. It is one of those diagnoses that may well astonish anybody who is not familiar with this particular condition.

Dr. Hassin mentioned the swelling and the vacuolization at the level of the compression of the cord and suggested that it was due to blockage at the cerebrospinal fluid outlet. The cerebrospinal fluid would seem to have an outlet at both ends, however, and I would like to ask Dr. Hassin whether some inflammatory and anemic changes in the cord itself might not account for those large spaces?

Dr. Israel Strauss, New York: In 1912, I read a paper before this association, the title of which was "Various Causes of Spinal Cord Depression." One of the cases cited was that of a man of middle age in whom, in opening the vertebral column because of compression of the cord (because it was thought there was a tumor), the surgeon came down on an extradural inflammatory process (really a pachymeningitis suppurativa) and did not do more than a laminectomy. The man recovered, regained considerable function, and the last I heard of him, he was doing very well.

Another case observed in the service two months ago was that of a young girl with severe pain in the upper dorsal and the lower cervical region, exquisite tenderness and high temperature. A lumbar puncture was performed; xanthochromic fluid was obtained with an increase of cells, and a block was also found. There was slight paresis of the lower extremities and within a few days this became a complete paraplegia. Because of the high temperature and the rapid development of paralysis, the surgeon was advised to perform a laminectomy; he cut down over the region that we thought was the seat of the trouble. He found

42. Ayer and Viets: Boston M. & S. J. **175**:865, 1916.

the vertebral column apparently normal and underneath it a pachymeningitis suppurativa, as was found in the other case just mentioned. The girl withstood the operation. I think she is still living, but she is completely paralyzed.

It is interesting in the two cases that I have seen—and I believe others also have described it—that as a rule one does not get a large collection of pus. A thickened dura is found and scattered throughout this thickened, inflammatory dura are small foci of suppuration. The surgeon in both cases wisely was content with merely exposing this inflamed dura, but did not of course attempt to open the canal and expose the cord.

In the first case, we did not find any focus from which the infection came. In the second case, however, there was a history of a furuncle in the neck, three weeks preceding the onset of the symptoms of inflammation in the cervical region.

Dr. William J. Mixter, Boston: This suppurative condition in the spinal canal outside of the dura has not been recognized in many cases. It is sometimes difficult to make a differential diagnosis when one exposes the inflammatory mass outside the dura in the type Dr. Strauss mentioned. It is difficult at first to tell multiple abscesses from a new growth. In my experience they have a better prognosis than the frank abscesses which Dr. Ayer mentioned. I have operated in three such cases and the patients have died. Of the others, I had one that lived and one that died.

Dr. Hassin: The spinal fluid was sterile; the microbe isolated from the abscess was reported to me as *Staphylococcus aureus.*

I am sorry that I did not know of the case of Dr. Ayer. The condition is by no means common, altogether about fourteen cases having been recorded.

As to Dr. Freeman's suggestion that the areolar spaces might have been due to anemic states, I wish to say that the latter may produce such areas, for instance, in subacute combined degeneration of the cord. But in anemic changes of the cord these areas are scattered throughout the length of the spinal cord, while in this case they were confined to the levels where the epidural changes were present. The changes affected the circulation of the spinal fluid and indirectly the discharge of the tissue fluids from the spinal cord. I discussed these problems in detail in my paper.

The perineuritis, a perineural inflammation of the roots, was the result of the epidural abscess, a suppurative inflammation. The latter successively involved the dura, subdural, pia-arachnoid and perineural spaces, thus interfering with the escape of the spinal fluid and tissue fluids of the cord itself.

COMPRESSION OF THE SPINAL CORD IN HODGKIN'S DISEASE

A CASE OF THIRTEEN YEARS' DURATION WITH RECESSION OF SYMPTOMS FOLLOWING ROENTGEN-RAY THERAPY *

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Compression of the spinal cord, with its resulting spastic paraplegia and level localizing sensory symptoms, of rather gradual onset, is so frequently due to tumor that other possible causative factors have received little consideration. Compression due to disease of the vertebrae is not uncommon and that due to localized disease of the meninges is known but rather rare. Still more rare is compression from disease of the epidural tissues such as has been known to occur in the lymphoplasias of the epidural lymphoid tissues in Hodgkin's disease.

Hodgkin's disease has aroused interest in many fields of medicine since it was first described by Thomas Hodgkin [1] in 1832. Clinicians and pathologists continue to discuss its etiology, and much has frequently been written in which the disease was regarded as infectious in origin. There is a remittent febrile reaction accompanied by general weakness, loss of weight, cachexia and lethargy. Associated with this febrile reaction is enlargement of the lymph nodes, and often the involvement of lymphoid tissue in many parts of the body. Many consider Hodgkin's disease to be neoplastic. The average duration of Hodgkin's disease is about three years, although Ziegler [2] stated that the disease may be of as short a duration as a few weeks. Cunningham [3] reported a case of twenty-five years' duration.

Hodgkin's disease was first described as a histologic entity by Sternberg [4] in 1899. The pathologic history in the lymphoid tissue consists of lymphocytes, mononuclear and multinuclear giant cells and, inconstantly, eosinophils in a connective tissue reticulum.

In 1902, Dorothy Reed [5] described the multinuclear giant cells as the characteristic histologic feature of the disease. These cells are known as Reed cells and are considered pathognomonic of the disease.

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* Read at the Fifty-Third Annual Meeting of the American Neurological Association, Atlantic City, N. J., May, 1927.

1. Hodgkin, Thomas: Med.-Chir. Tr. **17-18**:69, 1832.
2. Ziegler: Die Hodgkinsche Krankheit, Jena, Gustav Fischer, 1911.
3. Cunningham, W. F.: Am. J. M. Sc. **150**:868 (Dec.) 1915.
4. Sternberg: Centralbl. f. d. Grenzgeb. d. Med. u. Chir. **2**:641, 1899.
5. Reed, Dorothy: Johns Hopkins Hosp. Rep. **9**:133, 1902.

Glandular involvement is most commonly observed in the lymph nodes of the neck but the lymph nodes in the axillae, chest and pectoral and retroperitoneal regions are frequently involved. Symmers [6] stated that the disease may display itself in practically any tissue of the body, since minute collections of lymphoid cells are of wide distribution and, in Hodgkin's disease, lymphoid tissue is prerequisite to the development of the disease. Reed [5] stated that Hodgkin's disease seems to metastasize not by cellular transplantation but by causing a proliferation in preexisting lymphoid tissue, apparently anywhere in the body; also that the pathologic histology is the same in the dura and epidural tissues as in the lymph nodes of the neck, thorax or other parts of the body.

Many contributions have been published in which the studies were made on the basis of hundreds of cases, but rarely is there mention of the involvement of the central nervous system.

Welch [7] reported a case, with postmortem examination by Douglas Symmers in which the first sign of the Hodgkin's disease was a painless swelling on the right side of the neck. About two years later, a complicating paraplegia set in, and the patient died a few months following the onset of the paralysis. A piece of the lymph node on the right side of the neck was examined before death and a diagnosis of Hodgkin's disease was made. On postmortem examination, a collar of tissue corresponding in all essentials as observed by the naked eye to that described in the neck and abdominal lymph nodes was seen between the sixth and eighth thoracic vertebrae. This tumor mass was found to be entirely extradural. The underlying cord, however, was small and showed evidence of compression. Microscopic examination of the primary tissue in the neck, a nodule in the lung and the growth in the spinal canal all showed a similar structure, and it was concluded that the process belonged to the class of granulomas or Hodgkin's disease.

Ziegler [2] stated that granulomas of the dura mater may cause pressure of the spinal cord, giving rise to spastic paraplegia or there may be pressure on the columns of Goll and Burdach giving sensory signs.

Weber [8] recently published two papers on Hodgkin's disease in which the complicating or associating paraplegia is discussed clinically and histologically. In these two papers the author described a case of paraplegia with bilateral Babinski signs and sensory changes in the lower extremities and posterior pelvic region. Later, necropsy revealed a lymphogranulomatous growth attached to the outside of the dura mater over

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6. Symmers, Douglas: Am. J. M. Sc. **167**:157 and 313 (Feb. and March) 1924.

7. Welch, J. E.: Proc. New York Path. Soc. **10**:161, 1910.

8. Weber, F. P.: Quart. J. Med. **17**:1 (Oct.) 1923; Internat. Clin. **1**:126 (March) 1926.

the end of the spinal cord and further down over the cauda equina, accounting for the paraplegic symptoms present.

In these papers, articles by other authors were quoted by Weber in which were described cases of paraplegia associated with Hodgkin's disease, some with clinical symptoms without a postmortem examination and others with clinical symptoms and corroborative postmortem observations. Weber concluded that in advanced cases of undoubted Hodgkin's disease symptoms of paraplegia or cauda equina sometimes arise, also that the loose connective and fatty tissue in the epidural space between the dura mater and bone contain lymphatic elements in which it is not astonishing that lymphogranulomatous growth occasionally develops in Hodgkin's disease.

The following case of Hodgkin's disease was of about thirteen years' duration with a complicating paraplegia developing after ten years.

REPORT OF CASE

In a young man, aged 26, born in Russia and having resided in the United States during the fourteen years previous to entrance to the hospital, the present illness began in April, 1914, in his fourteenth year, with gradual onset. The symptom first complained of was dyspnea on moderate exertion. In May, 1914, he first noticed a small painless mass in the right supraclavicular region which rapidly grew larger, and soon there appeared a similar mass in the left supraclavicular region. On July 20, 1914, the patient was admitted to Mt. Sinai Hospital, New York. Examination of the blood made on the day after admission showed 13,000 white blood corpuscles, 44 per cent polymorphonuclears, 48 per cent lymphocytes and 8 per cent eosinophils. A biopsy report of one of the masses in the neck made by Dr. F. S. Mandlebaum was definitely indicative of Hodgkin's disease. The patient received thirteen roentgen-ray treatments, six to the left cervical region, six to the right cervical region and one to the right axilla. After his discharge from the hospital on Sept. 3, 1914, he received thirteen additional treatments. Following these treatments, he was free from symptoms or glandular enlargement for eight years.

On Jan. 24, 1923, he was admitted to the Jewish Hospital in Brooklyn, with a history of constant, dull, pressing pain in the abdomen, of nine months' duration, and the loss of 12 pounds (5.4 Kg.) in weight.

The physical examination at that time revealed a hard nodular mass in the epigastrium extending almost to the umbilicus. In the anterior axillary line, the mass was 6 cm. below the costal margin. A biopsy of a lymph node of the neck was performed on Feb. 9, 1923, by Dr. Lederer, who reported Hodgkin's disease. During this residence in the Jewish Hospital, six roentgen-ray treatments to the abdomen were administered, which cleared up the symptoms, and the abdominal mass disappeared.

The patient was readmitted to the hospital on Dec. 4, 1923, with the history of vague, shooting pains in the region of the shoulder blades, which began with a gradual onset during the latter part of October, 1923. The pains would radiate from the interscapular region toward the shoulders and also to the anterior thoracic region, where they were especially severe. In November, 1923, he began to complain of weakness in the lower extremities. This weakness became worse rapidly, and after six weeks he was unable to walk or stand. Intermittent

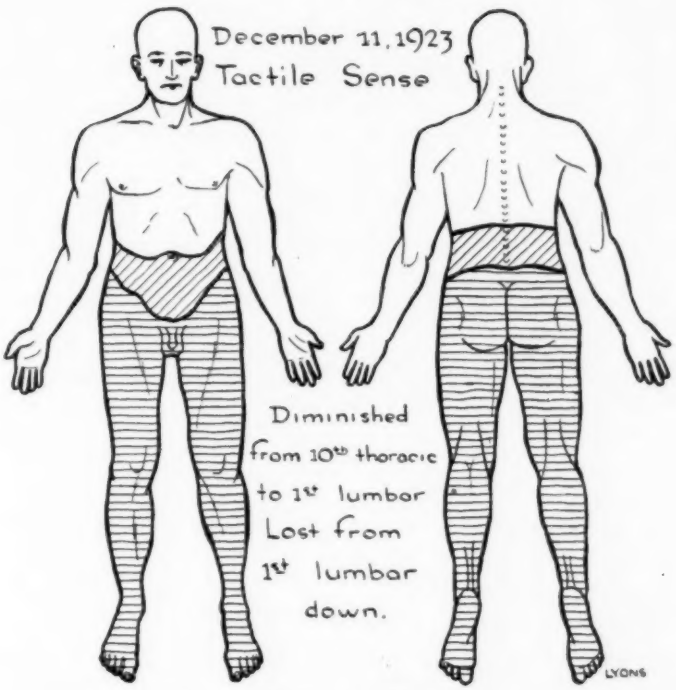

Fig. 1.—Compression level of cord.

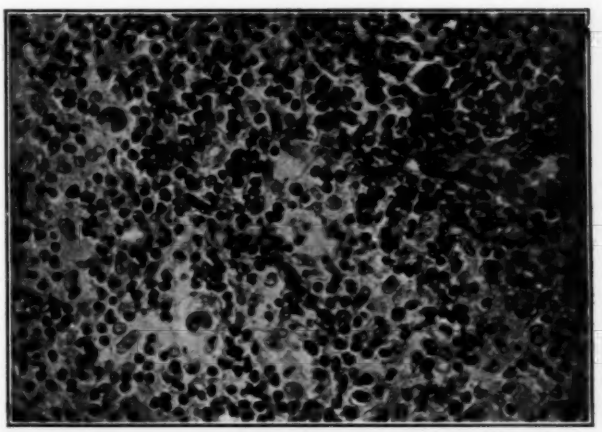

Fig. 2.—Lymphogranulomatosis of lymph gland.

priapism was present. Three days following the onset of inability to walk, the patient noticed a slight hesitancy in micturition; two days later there was retention of urine.

The neurologic examination did not reveal any involvement of the cranial nerve. The upper extremities were normal. There was a complete loss of motor power in the lower extremities and frequent involuntary muscular contraction in both legs. Pain and tenderness were not elicited on pressure over the vertebrae. The abdominal and cremasteric reflexes were lost. The patellar reflexes were present, with an exaggeration on the right side. The achilles reflexes were increased, with a transient clonus of the left ankle and bilateral Babinski sign. The sensory examination showed a band of hyperesthesia at the level of the tenth thoracic segment. Below this level there was loss of tactile sense. Pain and temperature senses were lost from the fifth thoracic segment downward. Vibratory and muscle-tendon sense was lost in the lower extremities. Examination of the spinal fluid showed 10 cells, globulin 3 plus, albumin 2 mm. ring and sugar 0.053 mg. per hundred cubic centimeters. The colloidal gold and Wassermann reactions were negative. A white blood count at this time showed 5,400 cells with 82 per cent neutrophils. The diagnosis

Comparative Study of the Blood Count

Date	Red Blood Cells	Hemoglobin, per Cent	White Blood Cells	Polymorphonuclears	Lymphocytes	Eosinophils
July 21, 1914	.....	...	13,000	44	48	8
July 22, 1914	6,816,000	108				
Jan. 25, 1923	4,700,000	80	16,600	79	21	0
Jan. 28, 1923	4,000,000	76	11,200	68	32	0
April 12, 1926	3,806,000	69	14,400	85	15	0

Bleeding, 1923, 4 minutes; 1926, 4½ minutes.
Clotting, 1923, 5 minutes; 1926, 5½ minutes.
Blood platelets, 456,000.

was "compression myelitis with paraplegia, due to lymphoid tissue disease, or Hodgkin's disease." The treatment advised was roentgen-ray therapy and, if no improvement in symptoms was observed, surgical intervention.

The patient was discharged from the Jewish Hospital on Jan. 22, 1924, unimproved, after having received one roentgen-ray treatment to his spine. He received three additional roentgen-ray treatments to the spine after leaving the hospital, and three months later he could walk with the assistance of crutches. In about nine months he was able to get about with the aid of a cane, but had considerable difficulty in locomotion from that time on.

On April 12, 1926, the patient was admitted to the Neurological Service of the Post-Graduate Hospital, with a complaint of weakness of the lower extremities, fatigability on moderate exertion and a loss of 15 pounds (6.8 Kg.) in weight during the four months before admission.

Neurologic examination revealed a slightly spastic gait. A Romberg sign was present. An ataxia of the lower extremities, greater on the left than on the right side, was observed. The deep reflexes showed a hyperactivity in the lower extremities. The abdominal reflexes were active and equal. There was a bilateral clonus, and the Babinski sign was present on the left and right sides. The general sensory examination revealed a diminution of vibratory sense in the lower extremities and an impairment of muscle-tendon sense in the toes of the left and right feet.

Physical examination showed a poorly nourished young man with many small, freely movable shotty glands in the neck. A few freely movable glands were seen in the left and right pectoral and axillary regions.

On April 20, 1926, a gland in the right axillary region was removed, examined and reported on from the laboratory as indicative of Hodgkin's disease. The Queckenstedt test done on April 22, 1926, did not reveal evidence of block. The spinal fluid was colorless and clear, with a normal globulin content, 14 cells per cubic millimeter. The Wassermann reaction of the spinal fluid was negative and the colloidal gold reaction was negative. The Wassermann reaction on the blood was negative.

At the Post-Graduate Hospital the patient received twelve roentgen-ray treatments with the filtered rays. These treatments extended from May 5 to Dec. 13, 1926. The left anterior thoracic region was treated three times, the left posterior thoracic region four times, the left axilla twice, the right anterior thoracic region once, the right posterior thoracic region once and the left cervical region once. The spine has not been treated at the Post-Graduate Hospital.

In December, 1926, he again reported to the hospital and a small nodule in the left supraspinatus region was discovered. Roentgen-ray treatment has been administered. His gait is still somewhat spastic and his neurologic signs have not changed since May, 1926.

SUMMARY AND CONCLUSIONS

When the patient was 14 years of age, an enlargement of the lymph node was first noticed in the right supraclavicular region; on biopsy the case was diagnosed as Hodgkin's disease. Following roentgen-ray therapy, the cervical lymph nodes disappeared. A remission of eight years followed, during which time the patient enjoyed excellent health. Then a constant, dull, aching pain set in in the abdomen, and physical signs revealed a large mass in the epigastric region and a few lymph nodes in the neck. After a second biopsy the case was diagnosed as Hodgkin's disease. Following roentgen-ray therapy, the mass in the abdomen disappeared and the symptoms were relieved.

About eight months later, sharp shooting pains radiated from the shoulder blades to the anterior thoracic region. Six weeks later, there was complete paraplegia with sensory change from the fifth thoracic level downward, and bilateral pyramidal tract signs in the lower extremities. After roentgen-ray treatments, the patient was able to take a few steps in about three months, and in nine months he got about with the assistance of a cane.

Two years later, he entered the Post-Graduate Hospital with a fever, increased difficulty in walking, weakness, loss of weight and large glandular masses in the left and right axillary and pectoral regions. Histologic examination of a gland from the right axillary region resulted in the diagnosis of Hodgkin's disease. Neurologic examination revealed some spasticity in gait, bilateral pyramidal tract signs and impairment of sensation in the posterior column in the lower extremities.

Roentgen-ray treatments were administered in the axillary, pectoral and cervical regions of the body, and the glands disappeared. The patient was advised to live in the country, and he gained 20 pounds (9 Kg.) in weight, his strength increased and his locomotion improved.

It is felt that the difficulty in locomotion at the time of his entrance to the Post-Graduate Hospital might have been due to the general weakness as a result of the general adenopathy, but the presence of localizing spinal cord signs indicate local involvement of the spinal cord.

The patient showed definite signs of compression of the spinal cord which receded under roentgen-ray therapy along with the general signs of Hodgkin's disease. Reports of necropsies in the literature prove that the lymphogranuloma of Hodgkin's disease can occur in the epidural space as a localized process. It seems fair to assume that this case of localized compression of the spinal cord in Hodgkin's disease can be explained in this way.

DISCUSSION

Dr. Howard C. Naffziger, San Francisco: I wish to add the experience in another case to that of Dr. Blakeslee.

Last fall, Dr. H. C. Moffitt of San Francisco referred a woman to me with a condition of complete paraplegia. She had suffered from Hodgkin's disease for five years. She had responded well to roentgen-ray treatment. For two years prior to the time that I saw her, she had occipital headaches which at first were thought to be due to some degree of arthritis in her cervical spine. Later on, continued observation showed disease of the bone, with involvement of the second, third and fourth dorsal bodies. This progressed, and with it, six months prior to the time I saw her, there set in spastic paraplegia, which became complete, with bladder difficulties. At that time the destruction of these vertebrae consisted of a scalloping out so that perhaps 50 per cent of the bodies were gone. During this time it became evident that the patient had become resistant to the roentgen ray, although previously her glands had responded well.

After the paraplegia had persisted for some two months, manometric readings revealed evidence of a complete block. A laminectomy was performed. The points of note were the marked lack of vascularity of the tissues and also the area of extradural involvement, part of it like mutton-tallow material, which could be scooped out readily, with relief of the marked dural compression. Following this, her sensory signs improved but she did not show any return of motor function.

About five months after the operation she developed a herpes zoster of the lower dorsal region, and with it encephalitis. Within two weeks after the subsidence of her herpes zoster the condition began to clear rapidly, and she returned home within a period of perhaps six weeks after the herpes zoster, and began to walk. The disease of the bone had not progressed; there was some increase in density about the previous area of scalloping. Since that time the patient has improved strikingly, with loss of practically all motor and sensory abnormalities. The regression of her trouble following herpes zoster was most striking.

Dr. Alfred S. Taylor, New York: One interesting variation in Hodgkin's disease extradurally might be worth mentioning. A young man, aged 26, had

in a period of six or eight weeks preceding operation developed signs of compression in the cervical dorsal region. A diagnosis of tumor of the spinal cord was made with the location in the cervicodorsal region. There was nothing else in the condition that would lead one to think of Hodgkin's disease at that time. He was operated on and an extradural tumor about 4 inches (10 cm.) long and three eighths of an inch (1 cm.) thick was removed from the median line, extending a little to each side of the median line. The dura was split and the cord was observed, but there was nothing abnormal about the cord, so the dura was closed. The wound was closed.

The material was taken to Dr. James Ewing for examination. It appeared very much like a fairly soft, fibrous material which stripped from the dura with relative ease. A week later, to my surprise, Dr. Ewing stated that it was a metastatic Hodgkin's deposit (he used the word "metastatic"), and that it was never primary, and he therefore advised us to look for Hodgkin's disease. The physician who had had charge of that boy for many years had never observed any evidence that would point to Hodgkin's disease. He went over the case again most carefully but could not find any evidence that would lead to a diagnosis of Hodgkin's disease. About six weeks later enlargement of the cervical glands appeared on both sides and the condition progressed in a perfectly typical way through the succeeding year to death in spite of treatment. It is interesting to note that the primary evidence of Hodgkin's disease may be found in the epidural space.

Dr. James B. Ayer, Boston: As to the rarity of Hodgkin's disease in the spinal canal, I want to report an undoubted, though unconfirmed, case at Massachusetts General Hospital this last spring. The patient developed an almost complete transverse lesion of the cord in the thoracic region. A spinal puncture showed xanthochromic fluid and complete block. Knowing that she had Hodgkin's disease, I made an attempt to administer roentgen-ray therapy; under that treatment she improved somewhat clinically. The point I wish to stress is that under that treatment the block disappeared.

Dr. Charles A. Elsberg, New York: I will add another case of a condition which has previously been supposed to be rare. We had a patient at the Neurological Institute who had verified Hodgkin's disease and who was treated for spinal symptoms by means of the roentgen ray in another institution. He suddenly became completely paraplegic and on account of the paraplegia I operated on him, but he did not improve after a wide laminectomy. Apparently lymphoid deposits in the epidural space of the spinal canal are not as rare as has previously been believed.

PHYSIOLOGIC HERNIATIONS OF THE BRAIN *

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ROCHESTER, MINN.

Herniations of brain tissue through small perforations in the dura mater have been reported infrequently since von Recklinghausen [1] noted the condition in 1870.[2] Several other cases [3] have been reported besides the ten summarized and discussed by Wojno [4] in 1912 and the fifty-one which Franz [5] (1926) recorded in a systematic study of 225 consecutive necropsies or 22.6 per cent.

In a study of the dura in fifty-nine consecutive cases at necropsy in the Mayo Clinic, so-called physiologic herniations of the brain were found in eleven cases, or 18.5 per cent. Table 1 summarizes briefly the type of case in which the dura was studied, the age of the patient and the occurrence of herniations in each group according to the age and the type of case.

In table 1, "other lesions of the central nervous system" include apoplexy, hydrocephalus, general paralysis, epilepsy, neurofibromatosis, etc. It may be noted in this table that herniations were found in the

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* From Section on Pathologic Anatomy, Mayo Clinic, Rochester, Minn.

1. Recklinghausen, quoted by Franz: Ueber multiple Hirnsubstanzhernien, Frankfurt. Ztschr. f. Path. **33**:72, 1926; by Wojno: Ueber physiologische Hirnhernien, ibid. **9**:279, 1912; by Prym: Ueber Gehirnhernien bei Hirndruck, Deutsche. med. Wchnschr. **2**:1145, 1923.

2. Recklinghausen (footnote 1), Schmidt, M. B.: Ueber die Pacchioni'schen Granulationen und ihr Verhältniss zu den Sarcomen und Psammomen der Dura Mater, Arch. f. Anat. u. Physiol. **170**:429, 1902. Wieland, E.: Der angeborene Weich- oder Lückenschädel, ibid. **197**:167, 1909. Weinnoldt, H.: Untersuchungen über das Wachstum des Schädels unter physiologischen und pathologischen Verhältnissen, Beitr. z. path. Anat. u. z. allg. Pathol. **70**:345, 1922. Loeschke, H., and Weinnholdt, H.: Ueber den Einfluss von Druck und Entspannung auf das Knochenwachstum des Hirnschadels, ibid. **70**:406, 1922.

3. Beneke, R.: Zwei Falle von multiplen Hirnhernien, Arch. f. Anat. u. Physiol. **119**:60, 1890. Blasius, O.: Ein Fall von Epidermoid (Perlgeschwulst) der Balkengegend. Zugleich ein Beitrag zur Kenntniss der multiplen Hirnhernien, ibid. **165**:504, 1901. Kyaw, quoted by Franz: Frankfurt. Ztschr. f. Path. **33**:72, 1926. Meyer, L., quoted by Wojno, ibid. **9**:279, 1912. Schmorl, quoted by Franz, ibid. **33**:72, 1926. Prym, P.: Ueber Gehirnhernien bei Hirndruck, Deutsche. med. Wchnschr. **2**:1145, 1923; Cruveilhier and Weiglein, quoted by Cushing, H.: Tumors of the Nervus Acusticus, Philadelphia, W. B. Saunders Company, 1917, p. 3.

4. Wojno, S.: Ueber physiologische Hirnhernien, Frankfurt. Ztschr. f. Path. **9**:279, 1912.

5. Franz, I.: Ueber multiple Hirnsubstanzhernien, Frankfurt. Ztschr. f. Path. **33**:72, 1926.

dura in the absence of any known intracranial abnormality. This fact is shown conclusively also in the work of Franz. Herniations were more frequent, proportionately, in such cases than in those associated with a cerebral lesion. Herniations were found in two of the eight normal cases, or 25 per cent, as compared to nine cases of the fifty-one associated with an intracranial lesion, or 17 per cent. The frequency in cases of tumor of the brain alone was 38 per cent. It may be concluded from these figures that no gross intracranial lesion bears a definite relationship to the production of physiologic herniations. To postulate a transient change in pressure [6] in the normal brain to account for the herniations would be hazardous.

Physiologic herniations have been described in detail by previous investigators. It may be stated briefly that after the dura is removed from the skull the hernias are usually found protruding from that surface which faced the bone; however, some are microscopic in size.

TABLE 1.—*Incidence of Herniation According to the Age and the Type of Case*

	Tumor of the Brain		Other Lesions of the Central Nervous System		Without Lesions of Central Nervous System	
Age, Years	Cases	Physiologic Herniation Found	Cases	Physiologic Herniation Found	Cases	Physiologic Herniation Found
0-20	7	3	6	1	1	1
21-40	3	1	3	.	2	.
41-60	8	3	17	1	3	1
61-80	.	.	7	.	2	.
Total cases..	18	7	33	2	8	2

Examination of the skull will often reveal the cavities in the bone in which these small formations found a lodging. The growths are generally nodular, rarely as large as 1 cm. in diameter, and are the color of cortical tissue and of similar consistence (figs. 1 and 2). There is little to add to the microscopic description already given by previous authors. The general picture (figs. 3, 4 and 5) is that of glial tissue (glial cell in an abundant stroma) with an occasional atypical nerve cell. The character of these nerve cells is not certain. They do not manifest the form or contour of any fully developed cortical nerve cell. It may be assumed that they are embryonal; but the presence of mild satellitosis suggests the possibility of a degenerative process as a forerunner of the condition as observed. The defect in the dura through which the herniation took place may be seen clearly in such sections; in some it is a cleanly punched-out hole, while in others it is less definite (figs. 3 and 5). The question as to whether there is a pial covering over the herniations has

6. Recklinghausen (footnote 1). Wieland (footnote 2, third reference). Beneke (footnote 3, first reference). Franz (footnote 5).

perhaps not been conclusively settled.[7] Pia cells cannot be demonstrated by a differential stain. However, at the periphery of some of these growths an occasional group of cells is found which closely resemble those of the pia-arachnoid. It is not certain whether these are rests or whether they are the remains of pial tissue torn from the surface during their removal.

It is not definitely known why physiologic herniations occur, although several factors have been thought to be more or less influential in their production. Herniations may not be present even though (1) congenital

Fig. 1.—Cranial aspect of the dura mater (case 1, table 2) showing physiologic herniations through the membrane in the portions lining the middle fossa of the skull.

defects are present in the pia and dura,[8] (2) a pathologic increase in intracranial pressure exists or (3) pacchionian granulations are present. It is significant also that these herniations are found in the dura covering the base of the brain and not in that of the convexity. Schwalbe's [9]

7. Wojno (footnote 4). Franz (footnote 5).

8. Wieland (footnote 2, third reference). Franz (footnote 5).

9. Schwalbe, G.: Ueber die Beziehungen zwischen Innenform und Aussenform des Schädels, Deutsches Arch. f. klin. Med. **73**:359, 1902.

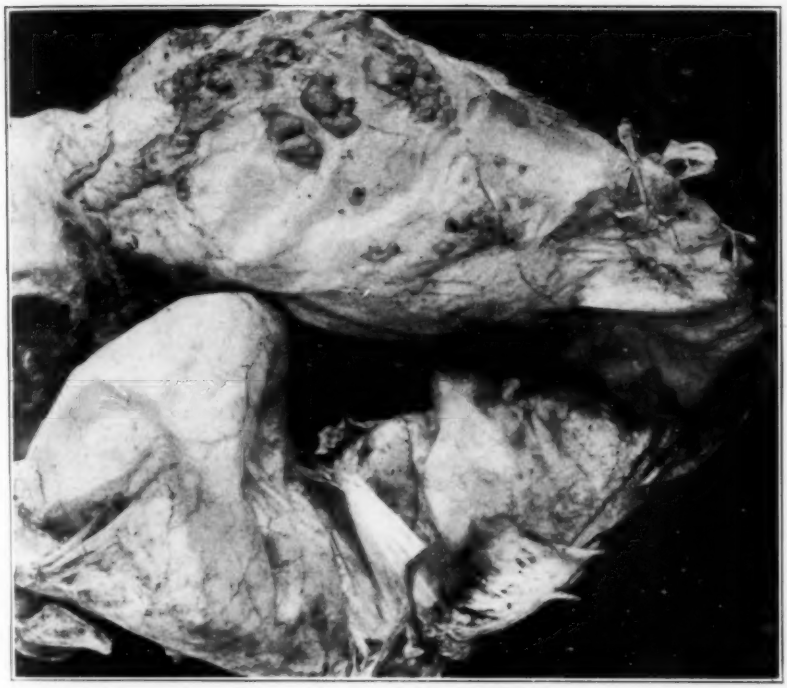

Fig. 2.—Cranial aspect of the dura mater (case 5, table 2) showing physiologic herniations through the membrane in the portions lining the middle fossa of the skull.

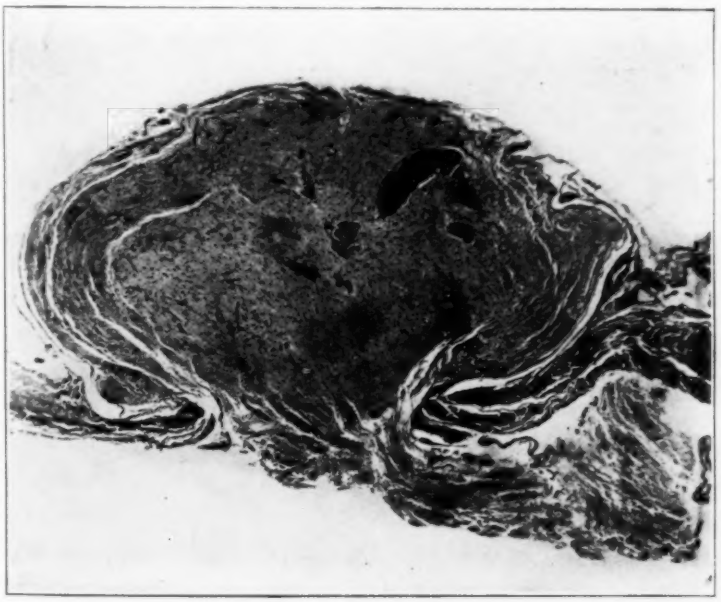

Fig. 3.—Herniation through a punched-out defect in the dura mater (case 3, table 2); $\times$ 18.

Fig. 4.—Details of structure of tissue in figure 3, showing chiefly glial cells and atypical nerve cells; × 350.

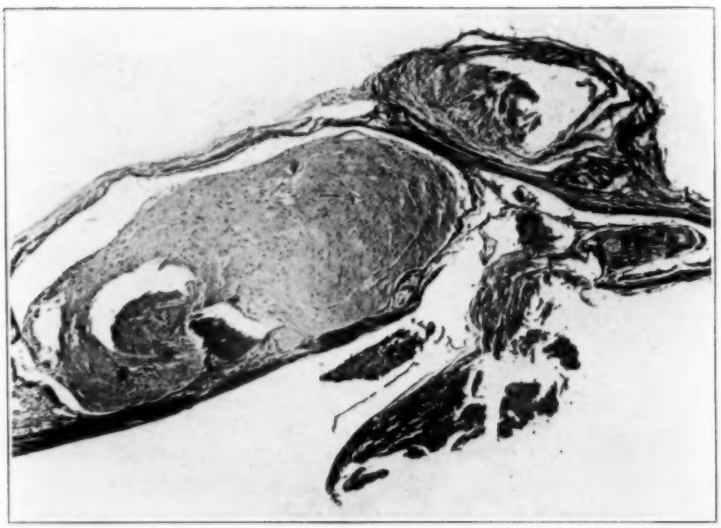

Fig. 5.—Herniations through defects in the dura (case 7, table 2). The dura in this case has apparently been split and lies in layers with the brain tissue between. Compare with figure 3; magnification, × 18.

theory in regard to the relationship of the weight of the brain to the inner cranial contour may be invoked, as suggested by some authors,[7] to aid in explaining this fact. Why herniations are present in some cases and not in others, even though all known etiologic factors are involved, is still an open question.

The cases of tumor of the brain in the present series were reviewed and tabulated to ascertain any influence on the presence of physiologic herniations of: (1) increased intracranial pressure; (2) duration of symptoms of tumors of the brain, and (3) age (table 2). The duration of symptoms could be estimated only approximately from the stated time of the initial symptoms such as headache, ataxia and convulsions. If there was any record of: (1) choked disks; (2) increase in pressure in the cerebrospinal fluid at the time of the spinal puncture, and (3) roentgenologic evidence of increased pressure the intracranial pressure was estimated as "increased," otherwise, as "normal."

TABLE 2.—*Physiologic Herniations in Cases of Tumor of the Brain*

Case	Age, Years	Approximate Duration and Symptoms of Tumor of the Brain in Months	Intracranial Pressure (Clinically)	Physiologic Herniations
1	51	84	Increased	Present
2	50	84	Normal	Present
3	37	24	Increased	Present
4	8	24	Increased	Present
5	55	18	Increased	Present
6	52	17	Increased	Absent
7	8	14	Normal	Present
8	44	12	Normal	Absent
9	11	8	Increased	Absent
10	48	5	Increased	Absent
11	41	5	Increased	Absent
12	7	4	Increased	Present
13	2	3.5	Increased	Absent
14	42	3	Normal	Absent
15	47	2	Normal	Absent
16	10	1.5	Increased	Absent
17	1	1.5	Increased	Absent
18	40	1	Increased	Absent

The data in table 2 are arranged in order of duration of symptoms; in case 1, they had been present for eighty-four months from onset until necropsy, and in case 18 for one month. The general conclusion from this summary is that age and pathologic increase in intracranial pressure seem to have no more marked relationship to the presence of herniations than to their absence. In eight of the eighteen cases reported intracranial pressure was increased and herniations were absent, while in five cases the pressure was increased and herniations were present. In the first five cases (those with longest duration of symptoms) physiologic herniations were present. In the sixth, in which herniations were evident (case 7), symptoms were of relatively long duration, but there was not a record of increased intracranial pressure. In the remaining case manifesting herniations the patient was a child,

aged 7 years; symptoms had been of comparatively short duration (four months) and intracranial pressure was increased. The duration of symptoms, therefore, apparently has a close relationship to the occurrence of physiologic herniations in this series of eighteen cases of tumor of the brain. The statement that (1) a pathologic increase of intracranial pressure has no definite relationship to the presence of herniations, and (2) the duration of symptoms of tumors of the brain seems to have some relationship are apparently paradoxical. This may be explained by the fact that such tumors as those in the cerebellopontile angle (as in case 1, table 2) may exist a long time, producing symptoms, but without clinical signs of increased intracranial pressure. Intracranial pressure may be increased in such cases without clinical evidence, and a theorist may adduce such a supposition to account for the herniations. There are no conclusive facts relative to this point.

Careful investigation of the history, symptoms and clinical record in the forty-one cases of the present series, other than those of tumor of the brain, produced nothing of consequence in the interpretation of the cause of herniation.

CONCLUSIONS

1. Physiologic herniations of the brain are met with in approximately 20 per cent of all cases.

2. The occurrence of physiologic herniations apparently bears no relationship to age or pathologic increase of intracranial pressure except in cases of tumor of the brain; in such cases the symptoms are of comparatively long duration.

THE ELECTIVITY OF DISEASES OF THE NERVOUS SYSTEM*

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Bacteriology has demonstrated that the specific nature of a tissue, when attacked by a morbific agent is of great importance in determining the evolution of the disease process. The conditions that influence the development of a disease include not only those of the individual constitution, but probably also certain superindividual peculiarities such as sex or race. Furthermore, it is evident that morbific agents have distinct affinities also for certain organ systems, and even parts of these systems, within an individual, a fact to be taken as the foundation of a symptomatically well-defined disease.

In attempting to explain these relations with the knowledge at present available, it must be recalled that the conception even of the individual constitution is not of absolute value. On the contrary, this constitution is an expression of varied and variable individual behavior toward the various surrounding influences. Hence investigations directed toward interpretation of the tendency of organs and organ parts to acquire characteristic lesions will offer the most fruitful results if they take into account not only the peculiarities of the substrate alone, but also those connected with the distinctive qualities of the morbific factors.

From this point of view I wish to discuss "locally predilective diseases of the nervous system." It is not possible to obtain a clear view of these complicated conditions, if one considers the properties of the nerve substance alone as sufficient causes of such different pathologic states. This, I believe, is the disadvantage of the so-called "Pathoklisis-Theorie" of C. and O. Vogt who sought to give a general explanation of these "predilective diseases of the nervous system" by assuming a peculiar physicochemical quality of the different parts of the nerve tissue.

Such a locally peculiar physicochemical nature indeed may correspond to quantitative and qualitative peculiarities of the metabolism of different parts of the nervous system; but their significance—as already pointed out—is not absolutely determined. Moreover "the causes hidden in the tissues" (P. Ehrlich) are not alone of a physicochemical nature. Finally, the term "pathogenesis" suggests that these investigations should include the time factor as well as that of local relations.

Study of these peculiar constellations reveals the following facts: Diseases of the nervous system occur without detectable external influ-

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* Read at a Meeting of the Chicago Neurological Society, Oct. 20, 1927.

ences; they include the various lesions on a heredofamilial basis. Some of them are probably produced by the morbific influence of inherited endocrinal or general metabolic disorders of unknown nature. At times these factors may affect a nervous system disturbed in its natural developmental tendency. The characteristic features of such diseases as amaurotic idiocy, Wilson's disease, pseudosclerosis and infantile non-inflammatory diffuse sclerosis of the brain have led to these conclusions. Little is yet known as to how their peculiar predilection in the nerve tissue takes place. In other presumably hereditary disorders of this kind the physiologic function as such seems to be the morbific influence itself. These diseases also suggest a qualitatively inferior natural tendency of the nervous system. According to Edinger, this group, marked by early wasting of systems, includes among others spinal muscular atrophy and hereditary spastic spinal paralysis. The latter has in common with the cerebellospinal ataxia (Pierre Marie), Pick's disease and Huntington's chorea (as Gans and Spatz proved in cases of Pick's disease), the central localization of the lesion in phylogenetically young parts of the nervous system. Another factor in the disposition to local diseases in later years are certain phases of the ontogenetic development of the nervous system; the development of certain parts of the nervous system in early embryonic life is more endangered than that of others. It will suffice to refer to malformations of the cord and maldevelopment of the central canal; syringomyelia and related diseases (Bremer) support this assumption.

But how is the special localization of diseases of the nervous system under the influence of various exogenous agents to be explained? What constellation of conditions, for instance, leads: to the localization of epidemic encephalitis in certain parts of the midbrain; to the accentuation of the morbid processes of Sydenham's chorea in the putamen; to Heine-Medin's disease, and still more to sporadic acute poliomyelitis in the gray matter of the anterior horns, and in the region of the motor nuclei of the cranial nerves; to the pathologic process in the posterior nerve roots and the posterior columns not only in tabes but also in pellagra, ergotin poisoning and other processes; to the elective characteristic diseases of certain peripheral nerve territories in diphtheria, lead poisoning, alcohol abuse and other noxae? At least it may be said that varied influences produce the peculiar localizations.

First may be considered the modus of the infection. The nervous system may be attacked by a noxa through the blood stream or through the cerebrospinal fluid. Spatz's investigations following the intravital dye accumulations of Goldmann have shown that the localization of the inflammatory changes in epidemic encephalitis, lyssa, Borna's disease of horses, gummatous cerebral syphilis, and of the lesions of the nervous

system following a meningitis arise by infection through the cerebrospinal fluid. The pathologic process in the posterior roots and columns in tabes also is, according to Spielmeyer's experiments in dogs infected by trypanosomes and his investigations on the effect of stovaine in the cerebrospinal fluid, supposed to be a result of a noxa attacking the spinal cord by way of the cerebrospinal fluid. The degenerative lesion of the optic nerve in tabes, originating from the periphery, as well as the pathognomonic lesion of circumscribed territories of the oculomotor nuclei, confirms this assumption. On the other hand, the different localization of the lesion of the brain in progressive paralysis points to a breakdown of the protective function of the mesodermic tissue, and therefore to an infection by way of the blood. These facts may be accepted as examples, but only in a general way, to show how the localization of an infection is determined by its course.

To learn the affinities of a noxa which has reached the nervous tissue by one or the other way within the limits of a specific disease, knowledge of the constitution and biologic effect of the noxa in question, as well as of the histologic, physicochemical and all biologic peculiarities of the substrate, is indispensable. Much is known about the histologic quality of the nervous system, but little about the noxae active in infectious diseases. A solution of this problem will more likely be found by starting from the effects of well known noxae which are fairly defined in respect to chemical composition and biologic effects. This starting point may be found in the effect of narcotics on the nervous system.

It is also important for this problem that narcotics—like other noxae—injure protoplasm in general, although this is more or less obscured by the different specific effects. According to Warburg, narcotics are adsorbed at the structure surfaces and alter the cell metabolism by disturbing their permeability. The specific affinity of these agents for the nervous system in general is explained partly by their higher concentration in the nervous system as a result of its particularly rich blood supply (Haggard). According to the investigations of Jensen, confirmed by Gayda, the blood supply of the brain per 100 Gm. per minute is sixty times as high as that of the muscles. Furthermore, as Alexander and Cserna have shown, the oxygen consumption per gram per minute in the brain is ninety times as high as in the muscles. On the other hand, the especially high lipoid content of the nervous system is believed to be one cause of these affinities. The importance of the adsorbing function of the lipoids in respect to narcosis, however, is not yet fully explained, since the so-called "Lipoidtheorie" of H. H. Meyer and Overton has been abandoned. Nevertheless, it is a fact that narcotic agents show a special affinity for nerve tissue. The importance

of the increase in concentration, of the higher rate of metabolism as well as of the adsorbing effect of the lipoids of the nervous system, may also be found with agents other than narcotics; for instance, the adsorption of lipolytic enzymes by brain tissue was proved by my own investigations.

It is well known also that narcotics operate differently on different parts of the nervous system. Kraepelin demonstrated a decrease of the sensorial simultaneously with an increase of the motor functions from the effects of alcohol. Sherrington explained the early effect of narcotics on superior centers by their action primarily on the "synapses." The central foci of conscious sensations and of movements and the long nerve paths with many synaptic intercalations may, for this reason, be affected before the regions of simpler reflex activity. Bumke explains the lack of reflex irritability of the pupils to light in tabes as a consequence of the especially great vulnerability of the optic reflex fibers as they spread out around the oculomotor nuclei. Contrary to the effect of narcotics, in tabes the primitive reflex mechanisms in the spinal cord are indeed especially early affected. But the usefulness of Sherrington's hypothesis—at least as a working hypothesis—is to be seen also in that, apparently, the long paths with their many synapses very often become disordered before the shorter ones. Schleich has suggested that the toxic effect of narcotics is a reciprocal of the phylogenetic age of different parts of the brain, a view confirmed to some extent by the conclusions of Fuehner who stressed the significance of phylogenetic development in relation to the effect of some noxae. With acute diseases, however, there is no proof for such a supposition.

The quantitative demonstration of a known noxa in certain parts of the nervous system might be of assistance in establishing a law of predilection. Thus strychnine, which chiefly acts on the spinal cord, can be found by biologic methods there alone. Investigations of that kind with narcotics and similar agents, however, have only complicated conditions. Pohl, Nicloux, and others, for instance, found the medulla oblongata, the pneumogastric nerve, the sympathetic nerve, and the phrenic unexpectedly rich in chloroform, though the function of these particular organs was least disturbed during narcosis. It is not assumed that a toxic agent like chloroform is decomposed especially at the place of its strongest effect—a matter that still needs investigation—one is surprised at these observations, the more so as the local application of a narcotic also has a local effect. Experiments on the sciatic nerve have explained the frequent palsy of the peroneus nerve preceding the paralysis of the tibial nerve. According to Albanese, this is produced by the peculiar anatomic localization of the peroneal fibers in the sciatic nerve. The elective localization of some infections or toxins in causing

palsies of peripheral nerves may be influenced by gross anatomic relations, but possibly also by more complicated metabolic processes. I will call attention only to the fact that normal physiologicochemical reactions, e. g., in an acting muscle, may be able to activate a latent

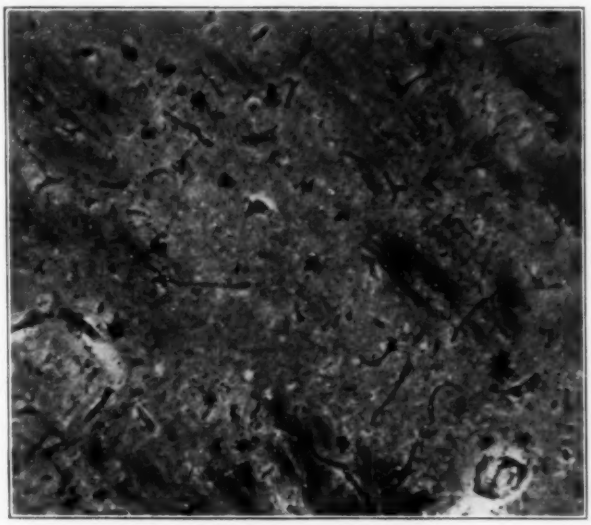

Fig. 1.—The capillary supply of the putamen.

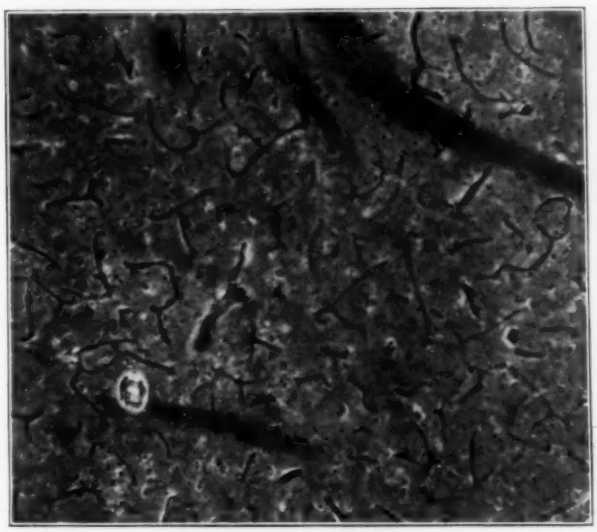

Fig. 2.—The capillary supply of the pallidum.

poison by newly formed metabolic products of the muscle, or its nerves. That matters are not simple is proved by the pathology of chronic lead poisoning, in which the almost elective palsy of the radial nerve is not necessarily peripheral, but, as indicated by the rather frequent fibril-

lations in the paralyzed territory, may be associated with a lesion of the anterior horns. Indeed, bulbar paralysis occurs in certain cases of lead poisoning.

Furthermore, it is important that noxae—at least those of a narcotic character—show a so-called "structure efficiency"; i. e., their effect manifests itself earlier on a more highly differentiated cell than on others. But of what kind are the characteristics of such higher differentiation? As to the histologic structure of the cells, practically nothing is known about the reciprocity between peculiarities of morphologic state and physiologic function. In other words, the peculiar affinities of narcotics,

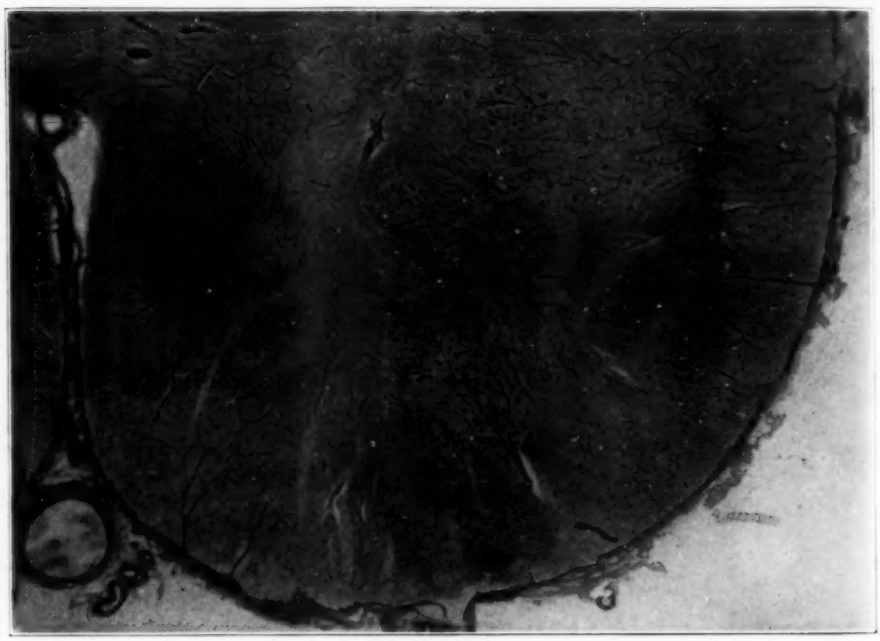

Fig. 3.—The ventral quadrant of the spinal cord in a horizontal section, showing the dense capillary network in the anterior horn and the scant amount of mostly cross-cut capillaries in the white columns.

as well as of other agents, may be so puzzling partly because histologic methods give only an incomplete picture of the biologically efficient structure of the cell and tissues. With regard to biologic behavior, as a symptom characteristic of the degree of differentiation of the cells, one might think that the amount of oxidation of a tissue is a criterion for its state of differentiation. Although the investigations of Winterstein and others showed no clear connection between narcosis and the degree of oxidizing processes, the high amount of oxygen consumed in nerve tissue may be an indicator of peculiar vulnerability of the nervous system. It is necessary to find other methods to establish parallels

between the chemical structure of a tissue and its vulnerability. In this connection one may recall the investigations of Ehrlich and Kobert who demonstrated the essentially antagonistic effect of lecithin and cholesterol toward various toxic agents, and the interesting experiments of Loewe on the antitoxic effect of different parts of the nerve tissues toward tetanus toxin.

The attempt to explain all the constellations of factors in the predilection of these diseases for the nervous system will encounter great difficulties, since the same noxa—even such a well known one as alcohol —may produce the most various, symptomatically unitary diseases.

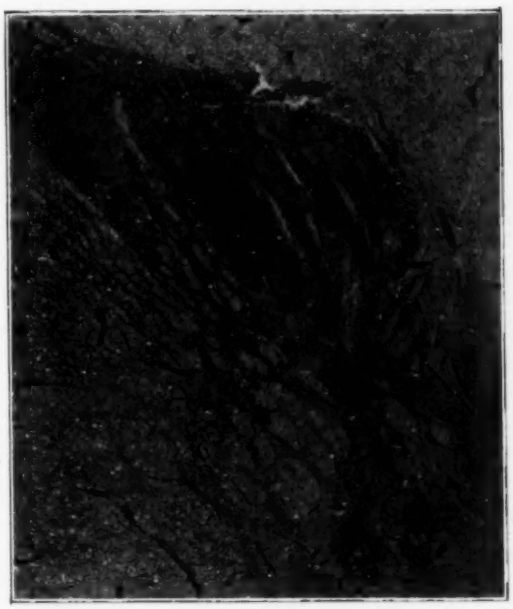

Fig. 4.—A cross-section through the posterior horn showing again the more intense capillarization of the gray matter but in the posterior horn as well as in the white columns the capillaries are mostly in cross-section.

On the other hand, my investigations have found a foothold in the fact that the abundance of blood vessels may express the state of nutrition of a tissue. I have succeeded in explaining some diseases of local accentuation, which Spielmeyer has collected together as "diseases of vascular type." It was evident that the local peculiarity of vascularization in various parts of the nervous system may be of decisive importance in regard to noxae affecting the vascular apparatus primarily. This involves less secondary effect of organic lesions, primarily vascular, than functional disorders of the blood supply; the importance of this was emphasized chiefly by Ricker and his associates, whose experiments are not yet fully grasped. As examples of the decisive

importance of the vascular supply, reference may be made to the elective disorder of the cornu ammonis which is observed particularly in epilepsy but also in other, even infectious, diseases; this has been explained heretofore as evidence of a peculiar "physicochemism" of this part of the brain. Spielmeyer has proved that this disorder is conditioned by an especially vulnerable nutrition that corresponds with the unfavorable vascular supply that arises from the peculiar development of the cornu ammonis. It is probable that the frequent predilection to disorder of the Purkinje cells of the cerebellum is also connected with peculiarities in the blood supply. From my own investigations, I have pointed out

Fig. 5.—A longitudinal section through the anterior column showing capillary network of predominantly horizontal course in the anterior horn and a mostly longitudinal course of the capillaries within the white columns.

that degenerative lesions in different parts of the brain, especially the characteristic softenings that follow carbon monoxide poisoning, are to be explained by the generally unfavorable arterial supply of the subcortical ganglia which is connected with an especially poor capillarization of certain parts of that gray matter. The photographs, figures 1 and 2, illustrate the conditions that obtain in the pallidum contrary to those in the putamen and need no further explanation.

The simple structure of the spinal cord is even more capable of showing the possible connection between locally accentuated disorders and the topography of the vascular supply than are the complicated vascular conditions of the brain. This is illustrated in figures 3 to 6.

The anterior spinal artery is seen in figure 3 in cross-section with vessels radiating into the cord from the vasa corona. The dense network of the capillary loops in the anterior horn contrasts impressively with the much more scant capillary supply of the columns. It will be noted also that, contrary to the course of the capillaries within the anterior horn, those spreading through the columns are mostly cut in cross-section. In contrast with the condition in the anterior horn, however, the capillaries within the posterior horn, as well as those in the columns appears chiefly in cross-section. This striking picture is confirmed by longitudinal sections through the spinal cord. Within the columns and

Fig. 6.—A corresponding longitudinal section through the posterior horn shows vessels in longitudinal section within the gray matter as well as within the columns.

in the posterior horn, but not in the anterior horn, the vessels are chiefly in longitudinal section and are taking, therefore, a course parallel to the columns.

The importance of these observations with regard to different pathologic cases is great. Even before making systematic investigations, attention may be drawn to the probable relation of some locally accentuated disorders of the spinal cord to these differences in the vascular supply of the various parts. For example, the accentuation of myelitic processes in the anterior horns, with no or only slight damage in the posterior horns, and the localization and kind of progress of myelomalacias within the columns undoubtedly point to some relation with the

peculiarities of vascular supply described. It should also be remembered that the blood stream in the spinal cord is essentially ventrodorsal. This fact may also be of some importance for pathogenetic studies of certain diseases of the spinal cord in the future.

These deductions afford only a glance at the different aspects of the problem—a problem as great as neurology itself. The most important part of the work in this field is yet to be done. It remains for the future to clarify the problem of predilection by improving old methods and finding new ones; in these, biochemic methods will rank higher than they have hitherto.

METABOLISM IN EPILEPSY

IV. THE BICARBONATE CONTENT OF THE BLOOD *

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The question whether persons who are subject to recurring seizures present abnormality of the acid-base relationships of the body is important. Certain considerations have recently brought the question to the fore. On the one hand, it has been shown that seizures in epilepsy may sometimes be precipitated by procedures which induce alkalosis, such as the administration of bicarbonate or by voluntary hyperpnea, and that tetany is accompanied by a condition of alkalosis. On the other hand, epileptic seizures may often be suppressed by procedures that induce acidosis, such as fasting, the use of a fat diet, the ingestion of acids or acid-forming salts, and breathing of a mixture rich in carbon dioxide. The last mentioned procedure may also be effective in relieving muscle spasm and hiccup. These various observations raise the question whether persons who are subject to seizures present any abnormality in the acid-base relations of the body.

Many earlier writers believed that epileptic persons present a decreased alkalinity of the body. This view is not supported by recent observations in which modern methods of analysis have been used. Because these reports have received critical review recently by Lennox and Cobb,[1] only a general summary need be given here.

With regard to evidence gathered from examination of the urine, Bisgaard [2] and his associates have published seventeen papers in which they reported that in patients with epilepsy there is a disproportionately large excretion of ammonia in the urine when compared with the excretion of nitrogen. Jensen,[3] Reiter [4] and Rafflin [5] found a few patients

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1. Lennox, W. G., and Cobb, S.: Epilepsy, from the Standpoint of Pathology, Physiology and Treatment, Medicine, to be published.

2. Bisgaard, A., and Nørvig, J.: Fortgesetzte Untersuchungen über die Neutralitäts Regulation bei der genuine Epilepsie, Ztschr. f. d. ges. Neurol. u. Psychiat. **83**:469, 1923.

3. Jensen, P.: Tre tilfoelde of orthoregulation ved den saakaldte genuine epilepsie, Hospitalstid. **68**:715 (July 30) 1925.

who did not show this "dysregulation." More recently Eriksen, Levinsen and Warburg [6] have shown conclusively that "dysregulation" is not a "condition unique" for epileptic patients nor is it constantly found in them. Various authors, notably Gamble and Hamilton [7] and Vollmer,[8] have found marked variation in excretion of acid with reference to convulsions, apparently as a result of the muscular work involved in the seizures.

The hydrogen ion concentration of the blood is the ratio between the acid and base substances in the blood. The earliest and most extensive observations concerning the hydrogen ion concentration of the blood in epilepsy were made by Geyelin [9] and by Bigwood.[10] The latter reported 380 measurements. These authors obtained values within the limits which are now considered normal (from 7.3 to 7.5). Within these limits, however, there was an abnormal degree of variation from day to day. Bigwood stated that as a rule seizures occurred on days when the blood was more alkaline. Essentially normal values were found also by Frisch and Fried [11] in 105 measurements made on twenty-three patients, by Marrack and Thacker [12] in eight patients, and by Dautrebande [13] in seven patients. In regard to the p_H of the spinal fluid, Osnato and Killian [14] obtained normal values in twenty-nine patients. Those obtained by Patterson and Levi [15] were abnormally alkaline, but this may have been due to the technic employed.

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6. Eriksen, K.; Levinsen, H., and Warburg, E.: Acid-Base Metabolism, Acta med. Scandinav. **65**:209 (Jan.) 1927.

7. Gamble, J. L., and Hamilton, B.: A Study of the Acid-Base Excretion of an Epileptic, Am. J. Dis. Child. **30**:587 (Oct.) 1925.

8. Vollmer, H.: Stoffwechseluntersuchungen bei Epileptikern, Ztschr. f. d. ges. Neurol. u. Psychiat. **98**:125, 1925; Ueber die Störung des säurebasen Gleichgwichtes bei genuiner Epilepsie, Klin. Wchnschr. **4**:1508 (July 30) 1925.

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10. Bigwood, E. J.: L'équilibre physico-chemique du sang dans l'épilepsie. L'ion calcium, J. de physiol. et de path. gen. **22**:70 and 94, 1924.

11. Frisch, F., and Fried, E.: Zur Frage der angeblichen Alkalose bei Epilepsie, Ztschr. f. d. ges. exper. Med. **49**:462, 1926.

12. Marrack, J., and Thacker, G.: Reaction of Blood in Epilepsy; Colorimetric Methods of Estimating p_H of Plasma, Brit. J. Exper. Path. **7**:265 (Oct.) 1926.

13. Dautrebande, L.: L'équilibre acide-base du sang dans l'épilepsie, Compt. rend. Soc. de biol. **94**:133 (Jan. 22) 1926.

14. Osnato, M.; Killian, J. A.; Garcia, T., and Mattice, M.: Biochemical Studies of the Blood and Spinal Fluid in Epilepsy, Brain **50**:581, 1927.

15. Patterson, H. A., and Levi, P.: The Spinal Fluid in Epilepsy, Arch. Neurol. & Psychiat. **15**:353 (March) 1926.

It is possible for the p_H of the blood to be normal and the acid and base radicals simultaneously either elevated or lowered. We therefore need to know the concentration of these various acid and base substances. In regard to the acid substances, chloride is the most important. It has been found in normal concentration in the blood of epileptic persons by Weston [16] (in ten patients), by Weeks, Renner, Allen and Wishart [17] (in forty-three patients), and by Sherrill [18] (in five patients). Hamilton [19] found normal values in both blood and spinal fluid in seventeen patients as we [20] have also in 100 patients. Of the other acid substances in the blood, normal values for the protein content of the plasma were found by Wuth [21] and for phosphates by Talbot and Moriarty.[22] The carbonic acid content of the blood closely parallels its bicarbonate content, which will be discussed presently. Organic acids and sulphates represent less than 2 per cent of the acid substances in the blood. Osnato et al.[14] recorded high values for lactic acid in forty patients.

Concerning the four bases found in the blood—magnesium, potassium, calcium and sodium—Blumgarten and Rohdenburg [23] found normal amounts in four patients. Hamilton [19] found the total base normal in seventeen patients. The facts concerning calcium are of considerable interest because of the recognized relation between low blood calcium and tetany. As a result of his large series of observations concerning the ionized calcium in the blood, Bigwood [24] believed that decreased concentration of ionized calcium (consequent on increased alkalinity of the blood) was the important factor in the precipitation of seizures. This view has not found support in the observations of Hamilton [19] (in seventeen patients), of Marrack and Thacker [25] (in six patients),

16. Weston, P. G.: Analyses of Blood of Insane Patients, Arch. Neurol. & Psychiat. **3**:147 (Feb.) 1920.

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of Osnato [14] et al. (in nineteen patients) and of us [20] (in 100 patients). These authors found normal concentration of calcium in both the blood and the spinal fluid of patients with epilepsy.

Ammonia has insignificant influence on acid-base relations in the blood. Bisgaard [2] regarded the finding of as much as 1.42 mg. in each hundred cubic centimeters of blood as important. More recently, Luck, Thacker and Marrack [26] obtained normal values in ten patients examined.

Sodium constitutes 92 per cent of the base of the blood. It may be measured indirectly as bicarbonate. In the absence of certain conditions which disturb the acid-base balance, such as abnormalities of respiration, measurement of the plasma bicarbonate gives a ready clinical method for determining the presence or absence of acidosis or alkalosis. The method usually employed measures the carbon dioxide combining power of the blood, or its "alkali reserve."

By the use of this method in seventy-three patients, Weeks, Renner, Allen and Wishart [17] obtained values between 54 and 64 per cent by volume, with an average of 59 per cent by volume. Frisch and Fried [11] found values between 43 and 78 per cent by volume in twelve patients, and Dautrebande,[13] values between 55 and 65 per cent by volume in seven patients. In the study of epilepsy there is need of observations from as large a series of patients as possible; therefore, we present certain data which we have collected during the last five years.

MATERIAL AND METHODS

Of the 100 patients examined, forty were inmates of the Monson State Hospital for Epileptics. The rest of the patients were attendants of the nerve departments of the Massachusetts General or Boston City Hospitals. Patients were unselected and were of both sexes and of various ages. In the main, seizures were without evident cause. In most instances, blood was taken before breakfast. Blood was centrifugalized soon after withdrawal and measurement of bicarbonate in the plasma made by the method of Van Slyke.[27]

RESULTS

The results obtained are displayed graphically by means of the accompanying chart. In this figure, the ordinates represent the concentration of bicarbonate in per cent by volume of carbon dioxide. Concerning the concentration of bicarbonate in the plasma of healthy persons there is no

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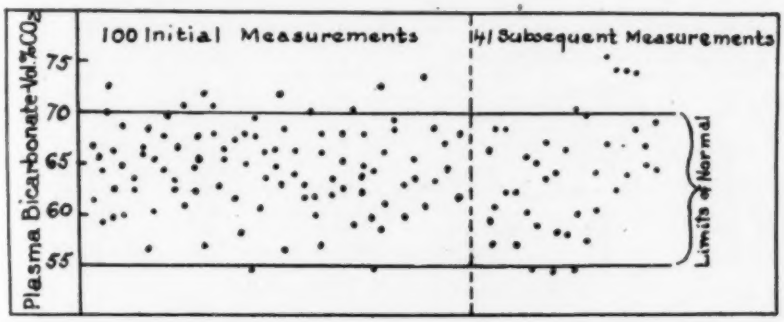
26. Luck, J. M.; Thacker, G., and Marrack, J.: Ammonia in Blood of Epileptics, Brit. J. Exper. Path. **6**:276 (Dec.) 1925.

27. Van Slyke, D. D., and Stadie, W. C.: The Determination of the Gases of the Blood, J. Biol. Chem. **49**:1 (Nov.) 1921.

unanimity of opinion. Palmer [28] stated that normal limits lie between 55 and 65 per cent by volume. Judged by this standard, three of the initial measurements were below and forty-six were above normal, so that only one-half lay within normal limits. If, as in the accompanying figure, one sets more liberal bounds for normal values—from 55 to 70 per cent by volume—one finds that only nine of the measurements were above this upper limit of normal. The average value for the whole group was 64 per cent by volume. This is 5 per cent by volume higher than the average measurement obtained by Weeks et al.[17] In the 100 patients that we examined, measurements of plasma bicarbonate were for the most part normal, but there was a tendency toward high normal values. Abnormal values were in the direction of alkalosis rather than of acidosis.

Blood for analysis was drawn without reference to seizures. It is possible that the reaction of the blood would be normal in the interval



One hundred initial and 41 subsequent measurements of plasma bicarbonate in 100 patients. The ordinate represents the carbon dioxide combining power of the plasma in percentage by volume. The abscissa is without significance. The horizontal lines mark liberal limits of normal. Of the initial measurements, nine are above and three below these limits.

between seizures but abnormal immediately preceding them. Tabulation of our data with reference to this point did not show a significant difference in the plasma bicarbonate of blood drawn within twelve hours of seizures and that drawn at other times. Measurements made from day to day in several patients did not show striking daily variation. In patient B. M., whose plasma bicarbonate was unusually high, measurements in percentage by volume made on different days were as follows: 73.6, 75.4, 74.1, 74.2, 73.9. Patient G. W.'s successive measurements were more irregular: 63.4, 62.6, 63.8, 68.5, 66.8, 65.0, 64.5.

On two occasions we secured successive samples of blood from patients having a series of seizures. Measurements of these samples

28. Palmer, W. W.: Acidosis, in Cecil: Textbook of Medicine, Philadelphia, W. B. Saunders Company, 1927, p. 598.

are shown in the accompanying table. In both instances, blood taken during convulsions contained a greater amount of bicarbonate than that obtained in the interval between seizures. The probable explanation for this lies in the fact that during the period of apnea and extreme venous stasis which accompanies convulsions, there is a great increase in the carbon dioxide content of the blood. To meet this increase in the acid substance, base is drawn from the tissues into the blood. Metcalf and Moriarty [29] found that during epileptic convulsions there is a definite shift in the p_H of the blood toward the acid side. Therefore, although the concentration of bicarbonate in the blood was increased, when compared with the concentration of carbonic acid it was relatively decreased. In a prolonged series of convulsions one would expect to find depletion of the alkali reserve of the blood. Blood from one of our patients who had been having serial convulsions for twenty-four hours contained only 35 per cent by volume of bicarbonate in the plasma. Fatal convulsions

Measurements of Plasma Bicarbonate With Reference to Convulsions

Patient M. H. (End of 14 Day Fast)			Patient R.		
	Plasma Bicarbonate, Per Cent by Volume of Carbon Dioxide			Plasma Bicarbonate, Per Cent by Volume of Carbon Dioxide	
Time		Blood Taken During	Time		Blood Taken During
8:30 p. m.	45.7	Interval	2:52 p. m.	57.8	Convulsion
10:30 p. m.	51.5	Convulsion	2:58 p. m.	50.9	Interval
2:30 a. m.	51.3	Convulsion	3:25 p. m.	56.1	Convulsion
8:30 a. m.	44.8	Interval	3:42 p. m.	50.3	Interval

were induced in a rabbit by means of an intravenous injection of camphor. The plasma bicarbonate before the injection was 40.8 per cent by volume. Blood taken before death contained 23.8 per cent by volume.

The evidence presented in the accompanying chart, together with that previously brought forward by other authors, demonstrates that patients who are subject to epileptic seizures do not show gross variation from the normal in regard to the alkalinity of the blood. The acidosis that occurs during convulsions is the result of the convulsions. Evidence concerning the beneficial effect of artificially induced acidosis on seizures in patients and in animals will be presented in subsequent papers. Such benefit cannot be due to the correction of an underlying abnormality in acid-base relations in epilepsy, at least so far as the blood is concerned. It is possible, of course, that there are acid-base changes in the tissues—particularly in the central nervous system—which do not find expression in coincident changes in the blood. This subject requires further research.

29. Metcalf, K. M., and Moriarty, M.: Blood Chemical Changes During Convulsions, Am. J. Dis. Child. **31**:65 (Jan.) 1926.

SUMMARY

Plasma bicarbonate has been measured in 100 patients with epilepsy. Three of these measurements were below 55 per cent by volume; forty-six were above 65 per cent and nine were above 70 per cent by volume. These data, as well as those presented by other authors, indicate that, in the main, patients with epilepsy show a normal condition of acid base equilibrium in the body fluids. Abnormality when present is in the direction of increased alkalinity.

CHRONIC SUBDURAL HEMORRHAGE

SUBDURAL HEMORRHAGIC CYST; TRAUMATIC PACHYMENINGITIS HEMORRHAGICA INTERNA; COMPRESSION TARDIVE, WITH REPORT OF CASES *

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The articles by LeCount and his associates,[1] published during the decade 1915 to 1925, emphasize the frequency with which intracranial hemorrhage in its various forms is overlooked as a cause of coma, and the infrequency of uremia compared with the number of instances in which such a diagnosis is made. A correct diagnosis of intracranial hemorrhage, however, may not be of greater value than an incorrect one of uremia if the cause of the hemorrhage and the location of the extravasated blood is not determined. It is important to distinguish between an extradural hemorrhage, as in rupture of the middle meningeal artery, an encysted subdural hemorrhage, as in the cases to be described, a primary subarachnoid hemorrhage, as in rupture of an aneurysm, and a primary intracerebral hemorrhage with secondary extension to the subarachnoid space. Skilful management depends on correct differentiation of these types.

My clinical experience with chronic subdural hematoma is limited to two cases in which the diagnosis was confirmed by operation, one probable case, and six or seven cases with allied pathologic conditions or symptoms. I have therefore utilized the histories of other reported cases and particularly the report of Sir Wilfrid Trotter [2] in the general description of the condition. The historical aspect is covered fully in the article by Putnam,[3] as is the production of bile pigment from intracranial hemorrhagic effusions.

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* Read before a meeting of the Chicago Neurological Society, Oct. 20, 1927.

1. Bissell, W. W., and LeCount, E. R.: A Consideration of the Various Forms of Coma, J. A. M. A. **64**:1041 (March 27) 1915; The Relative Frequency of the Various Causes of Coma, ibid. **68**:500 (Feb. 17) 1917. Holcomb, Blair: The Causes and Diagnosis of the Various Forms of Coma, ibid. **77**:2112 (Dec. 31) 1921. LeCount, E. R., and Guy. C. C.: The Clinical Differentiation of Spontaneous Intracerebral Hemorrhage and Uremia, ibid. **85**:200 (Dec. 26) 1925.

2. Trotter, Wilfrid: Chronic Subdural Hemorrhage of Traumatic Origin and Its Relation to Pachymeningitis Interna, Brit. J. Surg., 1914, p. 2.

3. Putnam, Tracy Jackson: Chronic Subdural Hematoma, Arch. Surg. **11**:329 (Sept.) 1925.

The incidence of subdural hemorrhage is unknown. In three large Chicago hospitals, the condition has been diagnosed thirteen times since 1914. Trauma was a factor in two cases. The diagnosis was confirmed by operation in two cases, by necropsy in two cases, and disproved in one case by operation, leaving eight unconfirmed diagnoses. Although not suspected clinically, subdural hemorrhage was discovered at autopsy in one case.

I attempted to compute the number of cases since 1914, because it was in that year that Trotter's report of four cases again called attention to the condition. At that time, he believed that it occurred more frequently than was generally recognized.

Cushing, in an introduction to a review of the subject by Putnam, said:

> Aside from the unhappily vivid mental picture of one unfortunate experience with a subdural hematoma under circumstances to be described, I confess to having had only the most vague recollections of previously encountering at operation any considerable number of the lesions under consideration. It consequently has been a surprise and the source of some mortification to find how many examples are buried under various titles in our past case histories.

The condition is so rare that it is seldom seen and only occasionally recognized. The report by Putnam, for example, is based on the presentation of a single case before the neurosurgeons of America; jointly they were able to add the records of only eleven cases to his study. On the other hand, Griswold and Jelsma [4] within five months observed four cases in which the diagnosis was confirmed by autopsy. They found the records of four additional cases in the files of the Louisville City Hospital.

Chronic subdural hemorrhage is invariably the result of trauma. The discovery of encysted subdural hematomas in persons with dementia paralytica and chronic alcoholism led older pathologists to express the view that the hemorrhage was secondary to inflammatory changes; hence the name pachymeningitis hemorrhagica interna under which it was formerly described. In more recent times, since it has been recognized clinically and since persons with it have been successfully operated on, its traumatic origin is more readily conceded. As Trotter points out, its frequency in persons with general paralysis and chronic alcoholism is exactly what might be expected, since they are particularly subject to cranial trauma as a result of falls. There are many records of death from intracranial hemorrhage of persons presumed to be recovering from the effects of acute alcoholism.

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4. Griswold, R. A., and Jelsma, F.: The Relationship of Chronic Subdural Hematoma and Pachymeningitis Hemorrhagica Interna, Arch. Surg. **15**:451 (July) 1927.

It has been characteristic of practically all the reported cases that the degree of trauma was not severe. Falls on the pavement, striking the head on some projecting object, glancing blows by falling objects and other forms of trauma to the head, often insufficient to produce cranial fracture or even a scalp wound, have been reported. Roentgenographic studies of all patients were not made so that unrecognized fractures may have existed in some. In two of my cases linear fractures were present, and in a third in which the diagnosis was unconfirmed the symptoms followed a fall, though fracture could not be demonstrated. In many of the reported cases, the patients resumed their activities immediately after the injury. One of the patients whose case will be reported here worked all day after the injury; another worked half a day; one was admitted to Englewood Hospital for treatment of lacerations of the scalp and was semiconscious when admitted. The history of trauma is important, but it is not always obtainable. In one of Trotter's cases, the history was not obtained until after the patient regained consciousness following operation.

The hemorrhage is supposed to result from tearing of the small veins which enter the tributaries of the superior longitudinal sinus. At the point at which the superior cerebral veins enter the sinus, the arachnoid is firmly adherent to the dura mater. This anchorage evidently protects the large veins and the sinus itself, while rendering the small vessels at its margin subject to stretching by displacement of the brain. Chronic subdural hematoma differs, therefore, from all other forms of intracranial hemorrhage in that it is of venous origin while the other forms are the result of arterial rupture.

Generally, the encysted collection of blood extends in an anteroposterior direction over the frontal and parietal lobes. It may be from 2 to 6 inches (5 to 15 cm.) in length and from a film-like layer to ¾ inch (2 cm.) or more in thickness. It is usually unilateral, but a few bilateral cases have been described. Rarely has it a basilar location. The blood lies beneath the dura but outside the arachnoid, and for this reason and because it becomes quickly encapsulated, the spinal fluid does not become bloody. Oppenheim [5] stated: "In doubtful cases lumbar puncture may enable one to decide. It is specially applicable to the traumatic form of the disease and has often placed the diagnosis on a sure footing." This has not been the experience of others nor of myself, if the statement means that positive evidence of hemorrhage is present in the spinal fluid. In practically all cases in which examination of the spinal fluid is reported the results have been normal, with an occasional case in which blood pigment only was present. If blood is found in the spinal

5. Oppenheim, H.: Text-Book of Nervous Diseases, trans. by Bruce, Chicago, Chicago Medical Book Company, 1911, p. 747.

fluid the condition is no longer a true case of subdural hematoma, since the subarachnoid space has been invaded. It is probable that free communication with the subarachnoid space would permit a majority of the symptoms to be relieved by simple spinal drainage. The significance of blood in the cerebrospinal fluid is an important point and is the basis of considerable discussion in neurologic literature. The capsule of the cyst of a subdural hematoma is often astonishingly tough, shows vascularization, is laminated and, depending on its age, may vary in color from dark brown to blue, green and straw color. The appearance and color of the contents of the cyst are likewise determined by its age. The contents may be a greenish, cloudy, semigelatinous fluid strongly suggesting an old abscess.

The symptomatology of chronic subdural hemorrhage of traumatic origin is extremely variable. Usually, immediately after the injury the patient begins to complain of headache, sleepiness, forgetfulness or vertigo. There may be lowering of efficiency, general stupidity, irritability and often a thick speech or aphasic signs. During this prodromal stage, which may last from a few days to several weeks, focal signs are not present. There may be general muscular twitchings, but jacksonian attacks are seldom observed. If the patient is kept quiet some of the symptoms may disappear entirely, although the headache is usually severe and persistent. The second stage is characterized by a sudden aggravation of symptoms. The headache becomes much worse and the drowsiness quickly passes into stupor. At this stage the respirations are deep and regular and resemble the profound sleep of a tired man. Periods of consciousness, of from only a few minutes' to several hours' duration, alternate with periods of unconsciousness. During the conscious periods, the complaint is always of headache; irritability is extreme; questions are answered slowly but intelligently. Vomiting does not constitute a major symptom, and paralysis does not occur. The periods of stupor gradually increase in length and finally merge into a profound coma. In this, the third stage, there may be changes in pupillary size and in promptness of reaction, but choked disk is not an essential sign even in the late cases. It was not present in my cases nor in the cases of Griswold and Jelsma. On the other hand, it was present very early in three patients with spontaneous subarachnoid hemorrhage whom I saw recently. Unilateral signs of cerebral compression are usually present, but a frank hemiplegia is rare. A moderate hemiparesis is much more common. The contralateral superficial abdominal and cremasteric reflexes are usually absent. A bilateral extensor toe response is often present with a unilateral lesion.

The diagnosis must be made at this stage as prompt surgical intervention is imperative. The results obtained in the treatment of coma

from any cause depend to a considerable degree on its duration. The longer it is permitted to exist, the less favorable is the prognosis. In four cases of Griswold and Jelsma, there was a history of trauma in three. Unilateral neurologic signs were present in all. In two cases coma continued for four days, in one for five days, and in one for six days before death occurred. In none of these cases was an attempt made to relieve the condition surgically. With prompt surgical treatment, the mortality in chronic subdural hemorrhage need not exceed the mortality in simple depressed fracture of the skull unless the hematoma is bilateral or basilar. The condition must be differentiated from other conditions which cause coma, particularly uremia. In both conditions, the pulse may be slow, the systolic pressure elevated and albuminuria present. If the nonprotein nitrogen of the blood does not exceed 50 mg. per hundred cubic centimeters, conclusions cannot be drawn in regard to the presence of uremia, because I have seen this concentration as a result of dehydration in a patient with tumor of the brain and normal kidneys. Fever may be present and may lead to confusion with one of the specific infectious diseases. The differentiation from the coma of diabetes is readily made, not by glycosuria, which may be present in both conditions, but by the presence or absence of the signs of ketonuria and the amount of blood sugar. In spontaneous intracerebral or capsular hemorrhages, the association is between coma and paralysis instead of between coma and paresis, and the history of the two conditions is unlike.

There is one condition following trauma, described recently by Naffziger,[6] in which the symptoms are identical with those of chronic subdural hematoma. He said:

> In some patients, increasing signs of pressure have caused us to perform a subtemporal decompression. The dura has been tense. When it is nicked with a knife blade, a jet of fluid has spurted out. This fluid is often water clear, but may be slightly tinged with fresh or old blood.

And again:

> It is worthy of emphasis that these subdural collections of fluid seem to represent a definite clinical group. Subdural fluid may be and is, sometimes, found with a slight degree of brain contusion or with some hemorrhage. Its presence, however, without other discernible pathologic changes, makes it of particular interest.

It is obvious from the reference to the presence of old blood that, in some instances at least, Naffziger was dealing with true subdural hemorrhage. These subdural serous effusions differ from the collections of

6. Naffziger, Howard C.: Subdural Fluid Accumulations Following Head Injuries, J. A. M. A. **82**:1751 (May 31) 1924.

fluid beneath the arachnoid of the brain and cord, which have been observed and described under the title of arachnoiditis. Localized edema of the brain itself may occur in the presence of nephritis with hypertension, causing headache, hemiparesis, choked disk and coma, and may be caused to appear and disappear by regulating the fluid intake and output, as in a case observed recently.

Spurrell [7] reports a case in which edema of the brain followed trauma, the symptoms of which resembled those of subdural hematoma. The patient was a woman who was struck on the right side of the head by a falling mirror. She did not lose consciousness, and external signs of injury were not present. For the following week she complained of headache and was dull and irritable. On the ninth and tenth days after the injury, she had several attacks of jacksonian epilepsy. A diagnosis of subdural hemorrhage was made. At operation, a moderate degree of cortical bulging was found and the whole of the visible cortex was markedly edematous, but hemorrhage was not found. This was edema of the brain and not a subdural serous effusion. She made an uninterrupted recovery and was well eight months afterward.

REPORT OF CASES

Case 1.—*History.*—A. C., a white man, aged 47, was seen in consultation with Dr. W. R. Abbott at the Englewood Hospital, the evening of Jan. 6, 1925. The family and previous personal history have no bearing on the case. While on his way to work on the morning of Dec. 23, 1924, he slipped on an icy sidewalk and fell, striking his occiput on the pavement. Immediately after the accident, there was bleeding from the nose for a few minutes. He felt dazed and complained of headache. Thinking that the headache would disappear, he reported for work as usual and worked until noon. The headache, instead of abating, became more severe and was felt in the temporal and frontal regions. Considerable vertigo was present. On arriving home, he vomited. Further vomiting did not occur throughout the duration of the illness.

On December 27, the fifth day of illness, he was seen for the first time by Dr. Abbott, who made a diagnosis of fracture of the skull and urged hospital care, which was refused. He was not seen again until December 29, the seventh day of illness, when he consented to enter the hospital for observation and treatment. He was still complaining of severe headache and of dizziness. Disturbances of speech, consciousness or of motor functions had not occurred. Roentgenograms of the skull showed a faintly visible linear fracture of the occipital bone. He was given sedatives, and in two days felt so well that he insisted on being up and about, although he still complained of headache.

On January 1, the tenth day of illness, it was noticed that his speech was thick and indistinct. During the day he slowly became unconscious and remained in this condition for a period of four hours. When he regained consciousness, his mind appeared to be perfectly clear. Temperature and pulse and respiration rates were normal. There had been no evidences of a convulsive seizure. Speech

7. Spurrell, W. R.: A Case of Traumatic Cerebral Oedema, Guy's Hosp. Rep. **74**:487, 1924.

continued indistinct, but he was not aphasic. From January 1 to January 6, periods of consciousness with sluggish mental reactions alternated with gradually lengthening periods of coma.

Physical Examination.—At 5:30 p. m., January 6, the fifteenth day of illness, the patient was in deep stupor, did not respond to questions or commands, and resisted examination. The heart, lungs, abdomen, urine, etc., were normal.

The pupils were equal in size, regular in outline, contracted, and reacted to light stimulation. Nystagmus and evidence of extra-ocular palsy were not present. A fairly satisfactory ophthalmoscopic examination did not show any evidence of choked disk. The face was symmetric. The tongue and pharynx were normal.

Hypertonicity of the muscles of the left side was present. Power of the muscles of the left arm and leg was diminished—determined by resistance to examination.

The tendon reflexes of the left arm and leg were slightly more active than those on the right. Clonus was not present. The superficial abdominal reflexes on the left could not be obtained, while those on the right were brisk. The left cremaster reflex was sluggish, the right brisk. There was normal plantar flexion on both sides.

The spinal fluid after puncture flowed drop by drop. Turbidity was not present. The Nonne and Noguchi tests were negative. The fluid showed 9 cells per cubic millimeter, 6 of which were red blood cells. The Wassermann and Lange tests, reported subsequently, were negative.

Diagnosis.—On the basis of the history of injury and the roentgen-ray examination, a diagnosis of fracture of the occipital bone had been made. On the basis of the neurologic symptoms, this diagnosis was enlarged to include increased intracranial pressure due to encysted hematoma in the right parietal region. Operation was advised.

Operation and Course.—The operation disclosed a large hematoma which was evacuated. The patient made a perfect recovery and did not present any defects at the time this paper was written.

Case 2.—W. W., a white man, aged 54, was seen in consultation with Dr. F. J. Lesemann at the Englewood Hospital, May 23, 1926.

On May 10, 1926, he was struck on the head by a brick which fell from a three-story building. At the time of admission to the hospital lacerations were present over the occipital region, blood was oozing from the right ear and the man was in a semiconscious condition. A small amount of emesis occurred, and general tremor of the body was present. The systolic blood pressure on admission was 120; four hours later it had risen to 166. Roentgenographic studies showed a fracture of the right lambdoid suture with a linear fracture extending into the mastoid.

The following day he was irrational; the urine contained albumin; the temperature by mouth was 100 F.; the pulse rate was 100 and the systolic pressure, 96. The third day he complained of severe right sided temporal headache. The temperature was 100.6; pulse rate 70; systolic pressure, 100, and white cell count 14,000. For the next ten days he constantly complained of headache; the temperature ranged below 100 F.; the pulse rate averaged 72; the systolic pressure varied from 114 to 128. At times he was irritable, irrational, and occasionally facetious. The right pupil was smaller than the left, and an ulcer of the right cornea developed. Trembling of the right foot was observed occasionally. On the thirteenth day, he was seen by a consultant for an insurance company who advised discharge from the hospital. On the fourteenth day, he was restless;

there was twitching of the right leg; the white cell count was 11,400; the pulse was slow and bounding; the systolic pressure was 145, diastolic 60. He complained of headache and kept turning the head to the left. A spinal puncture was made. The fluid was clear and contained 60 cells per cubic millimeter, mostly polymorphonuclear leukocytes. There was no improvement in his condition after the puncture, and he went into deep coma.

When I saw him, at about 10 p. m. on the fourteenth day, he could not be roused. The pulse rate was 60; systolic pressure, 145 and diastolic, 60; respiration deep, irregular and of the Cheyne-Stokes type. He was lying on the left side. The eyes showed no deviation; the left pupil was contracted, the right dilated; both were fixed. The retinal veins were congested on the left; those of the right side could not be seen owing to clouding of the media. There was no asymmetry of the face. The tongue was in the median line. There was a marked increase in tone of all muscles of the arms and legs, but the left side was definitely more rigid. The tendon reflexes were exaggerated, possibly those of the left side being a little more active. The superficial abdominal and cremasteric reflexes were absent on both sides. There was a Babinski sign on the right with no response on the left to any of the methods for bringing out a toe response.

Diagnosis.—On the basis of the general symptoms it was apparent that there was a great increase in intracranial pressure. The greater spasticity of the extremities of the left indicated a lesion on the right side. The absence of paralysis of the cranial nerves excluded a basilar lesion. The history of the conduct prior to the onset of coma did not suggest cerebellar involvement. On the other hand, the irritability alternating with facetiousness suggested a frontal lesion. The history of blood oozing from the right ear suggested the possibility of secondary infection but this was more than offset by the typical evolution of a case of subdural hematoma. A diagnosis of right frontal subdural hematoma was made, and one hour and ten minutes later a right osteoplastic flap was turned down.

Operation and Course.—In preparation for the operation 50 cc. of 30 per cent sodium chloride solution was administered intravenously. The dura did not bulge; it was darker than normal. When the dura was incised, a large clot extending well forward beyond the margin of the operative field was seen, which was scooped out without difficulty; drains were put in and the wound was closed. The shrunken condition of the brain produced by the hypertonic saline solution rendered the task of removing the clot much easier. The following morning the patient was conscious, and he was discharged from the hospital in good condition on the fifteenth day after operation.

COMMENT

Despite the fact that chronic subdural hematoma of traumatic origin was recognized and that surgeons successfully operated on patients for the relief of the condition as long as twenty-five years ago, it is surprising how much resistance one meets in attempting to establish the diagnosis. I have had one such experience in which the history and physical condition appeared to me typical of chronic subdural hematoma. Others, however, held to a diagnosis of thrombosis of the middle cerebral artery and would not consider surgical operation. In a doubtful case there is little to fear and much to be gained by prompt surgical treatment.

30 North Michigan Avenue.

DISCUSSION

DR. LOYAL DAVIS: The first case of this kind that I saw was at the Mayo Clinic when I was visiting Dr. Adson. A patient from a hospital for the insane had developed bilateral papilledema and other signs of increased intracranial tension. A lesion of the right frontal lobe was suspected. A ventriculographic examination was attempted but when the cannula was introduced a peculiar, thick greenish membrane was found lying just beneath the dura mater. Air was not injected, but an osteoplastic flap was made and a chronic subdural hematoma was found. Afterward, I saw three cases at the Peter Bent Brigham Hospital. Each of the patients had developed symptoms of increased intracranial tension which were inconstant in severity; in all, the symptoms followed a rather inconsequential trauma to the skull.

There are two points of interest to the surgeon in these cases. The membrane may cover an entire hemisphere and may occasionally be bilateral. While the hematoma is easily removed from the cortex the latter appears to ooze, and it is sometimes difficult to obtain a satisfactorily dry field. If the patient has symptoms of further increase in pressure after the operation, one is tempted to raise the osteoplastic flap on the supposition that more bleeding has occurred. Usually, the administration of hypertonic saline solution will reduce the postoperative edema, and the patient will show an uninterrupted recovery. These cases are more common than is generally believed and their amenability to surgical intervention makes it important to recognize them.

DRUG ADDICTION

A STUDY OF SOME MEDICAL CASES

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From the standpoint of origin, addicts may be divided into two classes: pure dissipators and those whose addiction resulted from medication.

The dissipators accidentally find that narcotics, especially opiates, have an agreeable effect on them, and they become addicted through indulging in quest of this effect. In medicinal cases the patients become addicted through the prescribing of physicians or by self-medication for some disease for which an opiate is apparently indicated. There has been a greater reduction in numbers of this type of patient than of the dissipators. The latter are more numerous, and in previous articles I have dealt chiefly with them. The basis of the study here reported was a survey of the personality and life history of a selected group of 119 medical addicts. It was undertaken in order to determine the special characteristics of this class of cases both as to susceptibility to addiction and the effects of narcotics in them.

The drug of addiction in 115 cases was morphine; in one, heroin; in two opium and in one, paregoric. Fourteen of the morphine addicts had taken heroin occasionally; one made a permanent change to heroin; sixteen, including six of those who had taken heroin, had also used cocaine for longer or shorter periods but none continued this drug indefinitely. One of the morphine users took the drug in the form of scopolamine, morphine and cactine pills, and one, a woman, occasionally indulged in scopolamine because she thought it increased the effect of her insufficient supply of morphine.

From information furnished me by the Narcotic Division of the Bureau of Internal Revenue concerning the seizures of narcotics illegitimately possessed and of purchases made in the collection of evidence as well as from the known limited territory over which heroin is used by addicts, it appears that the ratio of morphine to heroin addicts in this country is at least 6:1, and possibly as much as 8 or 10:1. The greater preponderance of morphine over heroin addicts in this series of 119 cases as compared with the general prevalence of the two types of addiction is due to several factors: (1) twelve of the patients were addicted before heroin came into general use in 1898; (2) sixty of them had practically always received their supply from physicians, and physicians almost invariably give morphine rather than heroin when they consider

it a duty to carry a legitimate addict; (3) there would naturally be fewer heroin addicts among medical cases, to which this study is confined, for the reason that heroin used therapeutically is less likely to cause addiction than morphine. This is chiefly because its therapeutic dose is much smaller than that of morphine.

There is practically no heroin at present available to physicians, owing to the law of June 7, 1924, which prohibits the importation of opium for the manufacture of heroin. However, no person in this series of cases was addicted to any drug after the supply of heroin was exhausted. It then happens that, during the period when both morphine and heroin were available, 103 of the addicts became addicted to morphine, one to heroin, and one of the original morphine addicts changed permanently from morphine to heroin. That more did not make this change was probably due to the fact that more than half of the entire number lived in territories in which heroin was not used by addicts.

Of the total number of addicts, 113 were white and six colored; seventy-four were men and forty-five women; seventy were addicted by physicians and forty-nine by self-medication. Eighteen of the latter received the first few doses of an opiate from a physician and then continued to buy the drug without his knowledge until they became addicted to its use. This naturally happened with greater frequency before than since the Harrison Law became effective in March, 1915. This law made it impossible for unlicensed persons to buy narcotics legally, except on prescriptions, and forbade the refilling of prescriptions containing narcotics. Of forty-one persons who were addicted after March, 1915, only eleven fell in the self-medication class and seven of these were possible dissipators, as will appear later. They were classed as medical addicts in accordance with the policy of accepting as such for the purpose of this study all who persisted in attributing their habit to medication.

There is a tendency for addicts who have taken treatments merely to please friends or to avoid the legal consequences of addiction to attribute the beginning of the habit to the necessity of some physical disease when the evidence points to dissipation as the real cause. This was true of seven of the eleven addicts already referred to. Four of these bought morphine from pedlers in this country after a short period of harmless legitimate opiate medication. The other three were ex-service men who were addicted by the same means in a country in which they said opiates could be bought without difficulty or danger. The thirty-eight who were addicted by self-medication before March, 1915, had from their own standpoint adequate reasons for it, either by virtue of prolonged illness or because of ignorance of the harmful habit they were slowly forming.

AGE

The ages of the 119 addicts at the time of examination ranged from 28 to 81. The average age was 45.7 years. The ages at the time of addiction ranged from 14 to 66, the average being 29.33 years. The ages at the time of addiction of those addicted since the Harrison Law became effective ranged from 20 to 61, the average being 32.9 years. The ages at the time of addiction of those addicted prior to the effective date of this law ranged from 14 to 64, the average being 28.09 years. Twelve of the entire number were 18 or under at the time of addiction, but only three who were addicted since the effective date of the Harrison Law were in this age group.

In another group of unreported addicts, including dissipators, a similar difference in ages is noted. In other words, this unreported group also indicates that, prior to March, 1915, the average age at addiction was about four years less than it has since become.

ADDICTION DOSE

The highest daily doses taken for as long as a month by the 116 users of morphine and heroin ranged from ⅝ to 35 grains (0.04 to 2.2 Gm.). The average was 12 grains (0.78 Gm.). Thirty-four of the addicts had taken 15 grains (0.97 Gm.) or more, and some had used these high doses for years. The average daily dose at the time of the examination was 7.66 grains (0.5 Gm.). There was a reduction in the dose in all but a few instances during the later years of addiction. This was brought about by the refusal of physicians to prescribe more than was absolutely necessary to maintain comfort, by the urging of narcotic inspectors and, in the case of those who had to resort to illicit sources, by economic pressure and the difficulty of securing small amounts regularly from pedlers. Except for these factors it appeared that most of the addicts would have increased rather than decreased the dose with advancing years.

The addicts who changed temporarily from morphine to heroin did not decrease the dose. In fact, I have observed that some morphine users who changed to heroin increased the number of grains in a few days. A possible explanation is that heroin has inferior addicting properties, and more of it is required to satisfy the physical craving produced by the continued use of a given amount of morphine.

CAUSES OF ADDICTION

The diseases or conditions given as causes of the original prescribing or self-medication are given in table 1.

In three cases the disease was not definitely determined. The remaining fifteen were accounted for by fifteen different conditions, most of

which were accompanied by more or less pain or discomfort. Among them was a case each of heart disease, diphtheria, typhoid fever and diabetes.

Most of the 119 addicts still had the condition for which opium was originally taken or they showed some residual of it and, with the exception of seven cases, there is no reason to doubt the previous existence of the alleged cause of the original opiate medication. The physical disease did not, however, furnish an adequate cause for the addiction in all cases. It led to the introduction to opium, but in most instances carelessness with or ignorance of the effect of opium or nervous instability was more important in leading to addiction than necessity for opiate medication.

TABLE 1.—*Causes of Addiction*

	Cases
Rheumatism, including two cases of neuritis and one of neuralgia	20
Diseases peculiar to women	12
Injuries	11
Tuberculosis of lungs	7
Tuberculosis of bones	3
Diarrhea and dysentery	8
Asthma	8
Migraine	5
Operations	5
Gassing and wounds received in army	5
Drinking	4
Gallstones	3
Carbuncles	2
Local infections	2
Yellow fever	2
Shell shock	2
Nervous breakdown	1
Insomnia	1

Nervous instability was an important causative factor. In another group comprising the general run of addicts I found that 86 per cent had an abnormal nervous make-up before addiction. In the present group eighty, or 67.2 per cent, of the entire number were definitely either neurotic or psychopathic before they became addicted. They started to use opium for the relief of what was often a self-limited physical disease and continued with it because it blotted out the unsatisfied cravings of an unstable constitution. It relieved them from a sense of inadequacy and the pressure of pathologic impulses, so that restlessness, discontent and feelings of inferiority were replaced by calm, contentment and a sense of efficiency.

Among the seventy-four men, thirty-three had been heavy drinkers before they became addicted to narcotics or between the time of cures and relapses. Twenty-five of the thirty-three had definitely been drunkards with histories of sprees, neglect of family, arrest for drunken-

ness, disorderly conduct while drunk, etc. The history of these inebriate characters was that they would take morphine several times to ease themselves off sprees until they found themselves taking it continuously; or, more often, they would take it for a short period for some minor physical disease, with the same result. Only one of the thirty-three continued to drink after he became addicted to morphine, and his drinking was then moderate. All of them resumed drinking when by cure of their addiction they abstained from narcotics for varying periods. It is of interest that sixteen of the definite drunkards were addicted by self-medication, and of the sixteen, nine had received the first dose from a physician. The instability that underlay the inebriety and not the drinking itself was the real cause of the addiction in most of these cases. Opium was accidentally found to satisfy the need that had been satisfied by whisky.

EFFECT OF PROHIBITION

The similarity of the basic motive for heavy drinking [1] and excessive indulgence in narcotics raises the question as to the effect of prohibition on drug addiction. The mere fact that drug addiction has decreased rapidly since prohibition became effective does not of itself prove that some drunkards have not turned to opium because of the difficulty of getting whisky. The effect that prohibition may have had was carefully studied in each of these medical cases as well as in numerous cases of the purely dissipated type of addict not reported here. The answer that the addicts often gave when asked about the causal effect of prohibition on their addiction was "If I could get dope as easily as I can whisky my troubles would be over." This answer is confirmed by a background of facts that clearly explains the reason why during the past ten years it is less common than it formerly was for drunkards to become addicts. The establishment of prohibition in 1920 did not change the situation, because narcotic regulation has grown stricter since then and it has become increasingly difficult for addicts to get narcotics either legally from physicians or illegally from pedlers.

Five drunkards in this series of cases were addicted to narcotics since 1920. One of these was a drug clerk who after opiate medication for a disorder of short duration helped himself to the proprietor's morphine; one was an old drunkard who contracted diabetes and was given morphine for it until he found he no longer needed whisky; one became addicted through having morphine prescribed for the drinking; one took it by preference following the prescribing of it for short periods after several operations, and one did the same following an injury. None of

1. Kolb, Lawrence: Types and Characteristics of Drug Addicts, Ment. Hyg. 9:300 (April) 1925.

the five was in any way influenced by difficulty in getting whisky. In fact, two of them, in attempting to cure their addiction because of the trouble it caused them, were drunk practically all of the time during several short periods of abstinence form morphine.

HEREDITY

The heredity as expressed by nervous difficulties in blood relatives, including only parents, grandparents, uncles, aunts, brothers and sisters, was studied in 118 of the addicts and was found to be tainted in sixty-nine cases and normal in forty-nine. The information gathered may be considered incomplete, as is the case with practically all studies of nervous heredity. In other words, complete information about the relatives of all patients would raise the proportion showing a nervous taint. The conditions that were considered to indicate a tainted heredity were organic nervous diseases, psychoses, definite functional neuroses, epilepsy, psychopathic personality and a strong family tendency to migraine, asthma or alcoholism. Apoplexy was not considered to be significant, and weight was not given to mere statements that relatives were cruel, domineering, miserly, queer or temperamental, because such statements are as a rule too unreliable to be used as definite evidence of defective heredity. The same attitude was taken toward ordinary drinking with occasional intoxication. Drinking was considered significant if it was more or less continuous, with repeated drunkenness, or was manifested by periodic sprees. Drug addiction was excluded as evidence of defective heredity because it was considered inadvisable to start a study of such addiction with the assumption that it indicated nervous instability. There were one or more additional addicts in nine of the families studied.

In order that the reader may appreciate more definitely the nature of the evidence on which certain families were considered to impart a hereditary taint, the following typical instances are cited from the material:

Case 1.—The father and two paternal uncles were drunkards; one brother had a psychotic attack, and one brother committed suicide.

Case 2.—The father was a drunkard and a brother, an epileptic.

Case 3.—The mother and sister have asthma; the mother had a severe nervous breakdown.

Case 4.—The father had migraine; a sister had epilepsy.

Case 5.—The mother was hysterical; an uncle and two aunts were psychotic.

Case 6.—The father had a nervous breakdown; the mother was psychotic and a sister hysterical.

Twenty-two cases of psychosis occurred in the families of sixteen of the addicts. Two more probable cases occurred in the same families, and one probable case occurred in another family. A case of epilepsy

occurred in each of seven other families, and one case of fits of undetermined nature in another family. Both asthma and migraine were important factors in the heredity of two families. Asthma was important in five others, and migraine in four others—but neither asthma nor migraine was the sole factor determining tainted heredity except in two of the patients. One of these had eight brothers and sisters with asthma, and the mother and sister of the other suffered with severe migraine. Organic nervous disease occurred in only two families.

Thirty-three of the addicts had definite drunkenness as part of the heredity, but drunkenness was the most important factor in the defective heredity of only ten of them. Of the twenty-five definite drunkards among the addicts, five did not have drunkenness in their antecedents and the heredity was normal in two.

INDUSTRIAL EFFICIENCY

The industrial efficiency was measured in all of these cases, the same criterion [2] being used that was used in classifying another series of addicts as to efficiency. Those who worked regularly and satisfactorily were credited with good or fair industrial records, allowance being made for short periods of idleness due to illness or inability to secure employment. Those who worked irregularly, owing to laziness, temperament, personality difficulties, drunkenness or prostitution, or who had long periods of idleness from any cause, were credited with poor industrial records. The industrial record was good or fair in ninety cases and irregular or poor in twenty-nine. The causes for the poor industrial records are given in table 2.

TABLE 2.—*Causes for Poor Industrial Records*

Drunkenness before addiction or during periods of abstinence	8
Conditions, including disease, incident to or following war service	5
Repeated attempts of neurotic persons to cure the addiction	6
Physical diseases	3
Prostitution	1
Asthma and neurosis combined with attempts to cure the addiction	5
Shutting off of regular narcotic supply	1

Following an injury that mutilated one arm the patient last mentioned in the table had taken an opiate and had worked on a farm to the best of his ability for forty-three years—until 1916. He then wandered from place to place looking for the morphine that he could no longer get at home.

2. Kolb, Lawrence: Pleasure and Deterioration from Narcotic Addiction, Ment. Hyg. **9**:699 (Oct.) 1926.

Seven of the poor industrial records are credited to patients who had a normal nervous constitution. One was the patient already described. Two owed their inefficiency to incidents, including sickness associated with war service; two to chronic physical diseases and two to attempted cures. One of the latter was also handicapped by asthma.

In studying the effects of opium on the efficiency of addicts, it is difficult to separate the effect of the drug itself from the effects of the disease for which it is taken and the psychopathic traits that make it so attractive to certain persons. There are some inadequate and shrinking personalities that are put at ease with the world by opium and are better able to face its problems because of it. Some neurotic persons who strive for efficiency and work well without opium are so soothed by it that they no longer feel the necessity for striving or working. Some pathologically restless persons who get into difficulties have their abnormal impulses toned down or regulated by opium, so that their normal impulse to work is not interfered with. It thus happens that some unstable persons are soothed and bettered by opium and some are soothed into an indifference that leads to idleness. Drunkards are much more likely to be benefited in their social relations by becoming addicts than any others. This is because they give up alcohol and get from opium the effect for which they were striving without being made drunk or vicious.

The effect of opium on the efficiency of the normal persons in this series was not measurable by the methods employed in the study. It is a reasonable assumption that there was some inhibition to activity that could have been appreciated by observing these persons at work for several years before and after addiction. Some listlessness and let-up in effort may be assumed in them because some psychopathic persons who have, however, taken enormous doses report such effects. Judged by the output of labor and their own statements, none of the normal persons had their efficiency reduced by opium. Twenty-two of them worked regularly while taking morphine for twenty-five years or more; one of them, a woman, aged 81, and still alert mentally, had taken 3 grains (0.19 Gm.) of morphine daily for sixty-five years. She gave birth to and raised six children and managed her household affairs with more than average efficiency. A widow, aged 66, had taken 17 grains (1.1 Gm.) of morphine daily for most of thirty-seven years. She is alert mentally but is bent with age and rheumatism. However, she does physical labor every day and makes her own living.

MARITAL RELATIONS

Seventy-nine of the addicts were married or widowed, twenty-five were separated or divorced and fifteen were single. Of the twenty-five separated or divorced, eighteen are listed among those having an unstable

nervous constitution, and it appeared that conduct incident to this instability was more important than the addiction in bringing about the marital infelicity. I [2] have discussed elsewhere the effects of addiction on marriage relations.

CRIME

Ninety of the addicts were never arrested during the entire course of their lives. The remaining twenty-nine were arrested a total of ninety-eight times for offenses more serious than traffic violations. Twelve of the arrests were for violations of narcotic laws, and eighty-six for other offenses. Most of the latter were made when the offenders were not using narcotics. Twenty-three of the addicts accounted for the eighty-six nonnarcotic arrests, the causes of which are listed in table 3. The arrests for drinking and fighting all occurred before the offenders became addicted or during periods of abstinence from narcotics. The

TABLE 3.—*Causes of Arrest of Addicts*

Drunkenness, or disorderly conduct while drunk	59
Fighting while drunk	3
Disorderly conduct, not drunk	1
Robbery	3
Stealing	3
Forgery	1
Prostitution	4
Bootlegging	4
Gambling	2
Nonsupport	1
On suspicion	5

inebriates accounted for seventy-one arrests, including three for robbery committed by one man. This man, a psychopathic patient and former drunkard, learned addiction on a prison farm while serving a term for robbery.

Only four persons classed as normal were arrested. One of these, a colored man with active tuberculosis of the spine and lungs, stole from the mails while working as a mail clerk. He had twelve fingers, and his psychic normality may be doubted. One, an apparently normal colored prostitute, was arrested twice for soliciting. One, also colored, was arrested for a narcotic offense, and the other one was the wanderer previously referred to who, after working regularly for forty-three years, left home in search of morphine because he could no longer get it there. He was arrested five times on suspicion.

The striking thing about the nonnarcotic offenses is the large proportion chargeable to drunkenness. It seems clear that the inadequate persons who seek relief by excessive indulgence in intoxicants or narcotics are much more serious problems as drunkards than as addicts. In fact,

some of the drunkards became orderly, law-abiding citizens after they abandoned whisky for opium.

The relation of the addiction of the offenders to their offenses was slight and accidental. Barring those arrested for violating narcotic laws, the wanderer was the only person in this group of addicts whose arrest was traceable directly to the narcotic habit, but the motive of two who stole may have been to secure the means to buy narcotics.

TREATMENT

Twenty-six of the 119 patients never took treatment, but some of them had made unsuccessful attempts to free themselves of the habit by gradual reduction at home. Only three of the twenty-six had ever found it necessary to deal with pedlers; the addiction of the remaining twenty-three had been considered so definitely legitimate that physicians did not hesitate to prescribe for them. I considered the condition of two of the twenty-six curable, and one of these has taken treatment since I examined him. In three other cases an attempt at cure was considered worth while, although two of the patients had been drunkards before addiction. Only two of the twenty-six untreated patients had poor industrial records, and in one of these the industrial inefficiency was due to a chronic, incurable physical disease.

Ninety-three of the patients had been treated a total of 320 times; the largest number of treatments taken by one patient was seventeen. I considered the condition of forty of the 119 patients curable, and thirteen of these have now been cured for periods ranging from eight months to two years. In ten other persons the advisability of administering treatment was considered questionable, while in sixty-nine treatment was considered to be contraindicated.

There is naturally a difference of opinion as to the advisability of attempting to cure certain addicts. It is desirable, therefore, to explain what is meant here by curable and incurable cases. From a medical standpoint, only the physical and mental well-being of the patient as directly influenced by opium or the lack of it should be considered in deciding whether any given addict should be treated. But the average addict labors under such serious and dangerous social handicaps that the possible effect of these on his general welfare must also be borne in mind. As a consequence of the enormous reduction in the number of addicts [3] that has occurred in recent years, knowledge of drug addiction has decreased and suspicion of addicts has increased. They are more and more regarded as depraved characters or even as criminals. Sym-

3. Kolb, Lawrence, and DuMez, A. G.: The Prevalence and Trend of Drug Addiction in the United States and Factors Influencing It, Pub. Health Rep. **39**: 1179 (May 23) 1924.

pathy for their weakness has been replaced in the public mind, and even in the minds of many physicians, by condemnation of their habit. Relatives often look on them as black sheep in the family. They find difficulty in securing employment. Physicians are loathe to prescribe for them. These addicts dread the day, which is always impending, when a regular supply of narcotics will not be available—and if they deal with pedlers, a prison sentence is possible. In view of these facts, it is considered desirable to cure every addict who could live comfortably without narcotics after periods of abstinence ranging as high as six months. As stated before, it is thought that forty of the addicts would do this, and it is believed that most of the forty would be benefited by permanent abstinence, although some of them would drink heavily and a few would be otherwise less efficient.

A not uncommon example of an addict, in whom early treatment could have forestalled later difficulties brought about by enforced abstinence after complete cure was impossible, may be cited.

This man, aged 74 years, had lived an efficient and useful life as an addict for forty-one years. Addiction was brought about by the use of deodorized tincture of opium for diarrhea which had lasted all one summer. He later changed to morphine and took 10 grains (0.65 Gm.) daily regularly for years. When he was examined, the spine was ankylosed and the neck bent sharply forward, due to a chronic arthritic condition which, however, no longer gave pain. Considerable edema of the legs was present, and he was generally feeble, although his mind was clear. Because of the infirmities, his earning power had naturally decreased greatly before the morphine had been withdrawn two years before examination. It then abruptly stopped because of the acute illness that followed. A certain amount of weakness continued after the acute symptoms subsided, due partly to periodic attacks of diarrhea which the patient attributed to lack of morphine. He felt that he could have continued to work at his profession if morphine had not been taken away from him, and that he could resume work and make some money if it were restored, but this seems doubtful. It is clear, however, that this old man was not benefited in any way by the enforced cure, and that he suffered because of it.

Only a few of the sixty-nine addicts for whom treatment was considered inadvisable would have been benefited even if the drug could have been successfully withdrawn; but there were other reasons in each case for advising against treatment. These reasons are: Long-standing addiction with continued physical diseases giving pain and discomfort is usually a contraindication to treatment of addiction. The same applies in a less degree to certain old persons in whom, on withdrawal of opium, pain returns and apparently persists in the site of healed lesions. However, permanent cures result from treatment in long-standing cases that are not complicated with asthma, migraine, epileptic or hysterical fits or other pronounced neurotic symptoms. In addicts with these conditions there is invariably an increase in the intensity of the symptoms during

and for some time after treatment. The increase in the number of fits is especially striking and discouraging. Opium should not be given for the conditions named because sufferers from them are especially susceptible to it. The drug is palliative for a time but never curative and in the end is harmful—after the patients have become strongly addicted to it, the treatments that so many of them undergo time after time cause intense suffering, reduce efficiency, and are seldom permanently effective. It is better, therefore, to let this type of addict alone.

Opium addicts with advanced, incurable pulmonary tuberculosis should not be treated for the addiction. Treatment adds greatly to their discomfort; it is sometimes dangerous and nothing is gained if the cure is effected. Addiction is contraindicated, however, in persons with curable pulmonary tuberculosis. It reduces the metabolic rate and lessens the chances of recovery from the tuberculosis, whereas successful treatment of addicts is followed by increased metabolic rate, increased resistance to infection, gain in weight and general improvement. The cough is increased somewhat during withdrawal of the drug, but there is no intense suffering compared to that which asthmatic addicts undergo during treatment and in a few weeks the cough is not any worse than it had been during the addiction.

COMMENT AND SUMMARY

In drawing conclusions from the observations of these addicts with medically induced cases it should be borne in mind that they represent a group from which the social and personal urge to cure has successfully eliminated many of the more normal members. They are therefore on the average more unstable, more antisocial and less efficient industrially and in the conduct of family relations than the original group would be. There is a larger proportion of former drunkards among them because inebriate characters who become drug addicts are not cured, as a rule, except by resorting to whisky or some other drug; and the drift of inebriates from opium to whisky was, when these cases originated, not as great as the drift from whisky to opium.

The group as it stands differs somewhat from the pure dissipators but has much in common with them. The dissipators are all abnormal and have no reason for addiction other than abnormal impulses and the accident of association, whereas 32.8 per cent of this group were normal and owed their addiction to the accident of disease. The remaining 67.2 per cent differ from the dissipators in that disease first brought them in contact with opium, but they are similar in that many of them owe their addiction, or the continuation of it, not to physical disease but to an abnormal susceptibility to the soothing effects of opiates.

Inebriates are common among both classes, but other types of psychopathic persons are more common among the dissipators. Neurotic, asthmatic and migrainous patients are more common in medical cases.

Only one of 119 medical addicts was addicted by heroin; this drug as used in medical practice is apparently much less likely to cause addiction than morphine.

The age at which persons became addicted in this and in another group of cases was four years greater after than before March, 1915.

In many of the cases ignorance, carelessness and peculiar susceptibility to narcotics due to nervousness were more potent factors than physical diseases in bringing about the addiction.

The average daily addiction dose of the morphine and heroin users decreased from 12 grains as a maximum to 7.66 grains. The decrease was due mainly to compulsion.

Thirty-three of the seventy-four men had been heavy drinkers, and twenty-five of these had been definite drunkards before they became addicted. Five of these drunkards were addicted after the prohibition amendment became effective, but the change to morphine was not due in any way to inability to get whisky.

The heredity in sixty-nine cases was tainted. Thirty-three of these addicts had definite drunkenness as part of the tainted heredity.

The industrial efficiency was good in ninety cases and poor in twenty-nine. Poor industrial efficiency was due mainly to drunkenness preceding addiction, physical diseases and nervous instability combined with attempts to cure the addiction.

Twenty-nine of the addicts were arrested a total of ninety-eight times during the course of their lives. Seventy-one of eighty-six non-narcotic arrests were of drunkards, and sixty-one were of drunkards who were not addicted to narcotics at the time of arrest but who were drunk. The one robber was a former drunkard who was convicted of robbery before he became addicted to opium.

Treatment for addiction was considered to be contraindicated in sixty-nine cases.

Clinical and Occasional Notes

ISOLATED PARALYSIS OF THE SERRATUS MAGNUS: REPORT OF A CASE*

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The serratus magnus arises by nine digitations from the outer surface and upper border of the eight upper ribs and from the aponeurosis covering the corresponding intercostal muscles. From these it passes backward along the wall of the chest to be inserted into the vertebral border of the scapula. Its function as a whole is to carry the scapula forward and at the same time to raise its vertebral border. It therefore takes part in the act of pushing. Its lower fibers move forward to the lower angle of the scapula and assist the trapezius in rotating the bone round an axis through the center of the serratus magnus; it thus assists this muscle in raising the acromion and supporting weights on the shoulder. It also assists the deltoid in raising the arm, as during this action of the muscle, it fixes the scapula and steadies the glenoid cavity. After the deltoid has raised the arm to a right angle with the trunk, by rotating the scapula, the serratus magnus and the trapezius raise the arm into an almost vertical position. When the shoulders are fixed, the lower fibers may assist in raising and everting the ribs.

The muscle is supplied by the posterior thoracic nerve, which is derived from the fifth, sixth and seventh cervical roots. Isolated paralysis is rare. Tournay and Kraus [1] quote Remak as stating that in a study of 12,000 cases of nervous disease only three cases of this form of paralysis due to any cause were found. Among the causes mentioned are: carrying heavy weights on the shoulder; lifting heavy weights; overuse of the arm; infections, such as typhoid fever, puerperal infections, measles and influenza, and exposure to cold. The possibility that a rudimentary cervical rib or enlargement of the last cervical transverse process plays a part has been mentioned. In one of the cases reported by Tournay and Kraus,[1] the latter condition was present. The reader is referred to their article for references to the literature.

REPORT OF CASE

E. S., a girl, aged 21, had always been healthy, except that she had had the acute diseases of childhood. Her work necessitated the lifting of heavy packages. About a month before coming under observation, she slept for two hours with her head resting on the left hand, the arm being in a flexed position. When she awoke, she was unable to elevate the left arm.

Examination showed that when she was at rest, the left shoulder was somewhat lower than the right. The left arm could be elevated above the horizontal position only with difficulty. In most cases, this cannot be done; when it can be done, it has been ascribed to the development of the middle

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1. Tournay and Kraus: Postinfectious and Isolated Paralysis of the Serratus Magnus, Arch. Neurol. & Psychiat. **7**:349 (March) 1922.

portion of the trapezius. When this movement is attempted, there is marked winging of the left scapula as shown in the illustration. All other movements of the shoulder and arm could be performed. The biceps and triceps reflexes were present on both sides; the biceps reflex was somewhat diminished on the left. The patient had not had pain, and there was no tenderness below the axilla. The report of a roentgen-ray study stated that "the transverse processes of the last cervical vertebra are somewhat prominent and may be causing some pressure." It could not be determined whether a reaction of degeneration was present or not. The presence of this reaction is spoken of by writers, but it seems to be extremely difficult to determine. In addition to the difficulty in elevating the arm and the winging of the scapula, the follow-

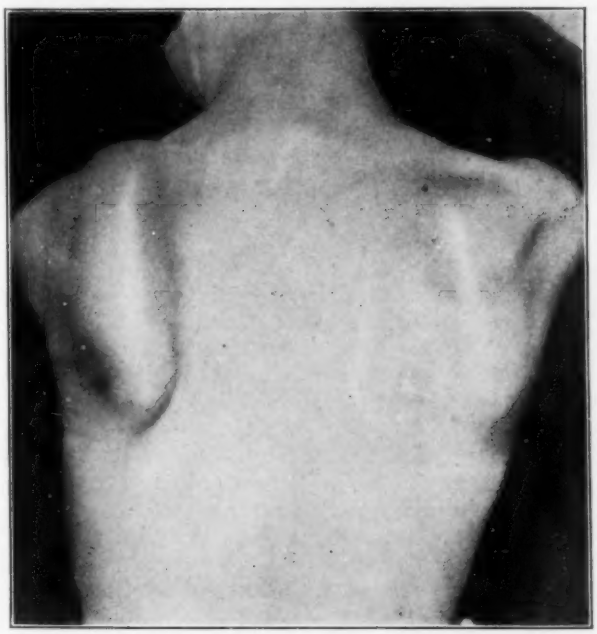

Fig. 1.—Winging of left scapula when attempt was made to lift arm above the horizontal position.

ing symptoms which denote isolated paralysis were found: The sternocleidomastoid and trapezius were more forcibly contracted on the paralyzed side when the arms were abducted. When this was done, the outline of the axilla was rounded and not angular as on the normal side. The chest on the affected side was three fourths of an inch smaller than on the other. When the shoulders were lifted forcibly, the supraclavicular fossa on the affected side was narrower and deeper than on the normal side. The scapula on the paralyzed side was nearer the midline; in trapezius paralysis, it is farther away. There seemed to be a slight scoliosis. The distance from the deltoid to the trapezius with the arms abducted was one-half inch more on the affected side. When the shoulders were shrugged, the distance from the deltoid to the sternocleidomastoid was 1 inch less on the paralyzed side.

A point of interest in this case is that, with the exception of one, in all reported cases the condition has been on the right side; this is, therefore, the second case in which it occurred on the left.

COMMENT

Infection can probably be ruled out as a cause, although a few cases have been attributed to an unknown infection. The three factors of lifting heavy weights, enlarged transverse process of the last cervical vertebra and holding the arm for a long period in a strained position may each have played a part in the etiology of the case reported. There has been some improvement since the onset of this trouble.

NOTE.—Since this article was written, the patient has practically recovered. This is very unusual, the prognosis for recovery being regarded as bad.

2018 Chestnut Street.

PUPILLARY ANOMALIES IN SCHIZOPHRENIA*

WILLIAM C. MENNINGER, M.D., TOPEKA, KAN.

Certain anomalies in the regularity, equality and reaction to light of the pupils of the eyes are established stigmas of a neuropathologic condition, especially of neurosyphilis. That these anomalies may have other significance is also recognized, however; and because of what seemed to be a frequent occurrence of such independent or idiopathic pupillary pathologic changes, I[1] made a previous attempt to determine the relative frequency of their occurrence and the relative frequency of a definite indication in 1,000 general medical and surgical cases. In approximately one third of these cases there was no apparent cause for the anomaly and no other associated pathologic condition. From a study of these cases it was suggested that such iodiopathic pupillary anomalies might represent stigmas of an inferior constitutional development or of deteriorating somatic changes, without special diagnostic importance. Because of the high frequency of the occurrence of somatic stigmas in schizophrenia, a series of 400 patients with long standing and well established cases of dementia praecox have been studied to determine the frequency of pupillary inequality, irregularity and impaired light and convergence reflex.

The persons examined were taken from the "chronic wards" of St. Elizabeth's Hospital, and with few exceptions their cases conformed, at the time of the pupillary observation, to the classic hebephrenic dementia praecox of Kraepelin, although the original cross-section at admission may have been catatonic or paranoid in some cases. In most instances these patients have been observed over a period of years. Cataleptic patients were not included because, as has been noted by others, the cataleptic state may bear a direct relation to the pupillary reactions. Patients over 60 years of age were also excluded from the group because of possible senile changes.

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*From St. Elizabeth's Hospital, Washington, D. C.

1. Menninger, W. C.: The Frequency of Pupil Anomalies in General Medical and Surgical Cases, J. Kansas M. Soc. **26**:282, 1926.

THE PUPILS IN DEMENTIA PRAECOX

In 1906, Bumke[2] described the absence of a triad of pupillary reactions in 60 per cent of patients with dementia praecox in the Freiburger Clinic: "psychic reflex, pupillary unrest, and reflex dilatation on sensory stimulation." By the psychic reflex, he refers to the pupillary reaction on psychic stimulation (fear, anger, etc.) and by pupillary unrest, the normal oscillation of the iris. He regarded this diagnostic triad as almost pathognomonic of early dementia praecox, and many subsequent writers have confirmed his observation—Bach,[3] Huebner,[4] Sioli,[5] Wassermeyer,[6] Weiler,[7] and others. In 1907, Westphal[8] described "katatonische Pupillenstarre" in catatonic stupor: a transient loss of the light and convergence reflexes, sometimes in one eye and then in the other, sometimes in both, as well as changes in the outline of the pupil from oval to

TABLE 1.—*Summary of Important Recorded Pupillary Anomalies in Dementia Praecox, in Percentages*

Author	Number of Cases	Dilatation	Contraction	Inequality	Irregularity	Disturbed Light Reflex	Argyll Robertson Pupil
Blin: Rev. neurol. **14:** 151, 1906	87	20.0	7.0	19.0	....	5.0	13.8
Zablocka: Allg. Ztschr. f. Psychiat. **65:** 318, 1908	403	9.9	4.2	10.0	....	14.2	....
Tyson and Clarke: J. A. M.A. **50:** 1415 (May 2) 1908	85	....	....	....	....	16.5	....
Chardinal and Guimaraes: Arch. brasil. d. psychiat., 1908, vol. 4.	116	....	....	....	....	....	18.0
E. Meyer: Allg. Ztschr. f. Psychiat. **66:** 845, 1909	383	8.6	10.0	12.5	....	11.7	"a few"
Raecke: Arch. f. Psychiat. **47:** 1, 1910	200	....		"26 cases irregular or unequal"			
Reichmann: Arch. f. Psychiat. **53:** 302, 1914	215	28.3	6.0	13.9	21.8	70.0	3.7
Frith: J. Ment. Sc. **60:** 82 and 224, 1914	27	....	....	33.0	50.0	11.1	....
Knemeyer: Inaug. Diss., Königsberg, Otto Kummel, 1915	168	33.0	12.0	14.0	10.0	50.0	....
Rahne: Inaug. Diss., Kiel, H. Fiencke, 1916.	80	5.0	....	14.0	39.0	12.0	2.0

2. Bumke, O.: Pupillenstörungen bei Geistes- und Nervenkrankheiten, Jena, G. Fischer, 1906.

3. Bach, L.: Pupillenlehre. Anatomie, Physiologie und Pathologie, Berlin, S. Karger, 1908.

4. Huebner, A. H.: Untersuchungen der Pupillenreaktionen auf psychische und sensible Reize, Arch. f. Psychiat. u. Nervenh. **41:**1016, 1906.

5. Sioli, F.: Ueber die A. Westphal'schen Pupillenstörungen bei Katatonie und die Pupillenunruhe und sensible Reaktion bei Dementia praecox, Neurol. Centralbl. **29:**520, 1919.

6. Wassermeyer: Zur Pupillenuntersuchungen bei Geisteskranken, Arch. f. Psychiat. **43:**124, 1907.

7. Weiler: Pupillenuntersuchungen bei Geisteskrankheiten, Allg. Ztschr. f. Psychiat. **63:**572, 1906.

8. Westphal, A.: Ueber ein katatonischen Stupor beobachtetes Pupillenphänomen, Deutsche med. Wchnschr. **33:**1080, 1907.

round and the reverse. Many subsequent observations have demonstrated temporary loss or slowing of the reaction in many cases. On the basis of this work, the opinion was not infrequently expressed that dementia praecox was to be regarded as an organic disease. Meyer's work, first published[9] in 1910 and elaborated[10] in 1912, showed that changes in the pupillary reaction, even to complete inactivity, can be induced by localized abdominal pressure. In 1914, Reichmann[11] investigated the subject in 215 cases of dementia praecox and concluded that a definite explanation is not yet determined; but as a working hypothesis, it appears probable that there is a connection between certain vasomotor disturbances and disturbances of the innervation of the iris.

From 1910 to 1915, the primary interest in pupillary observations in dementia praecox centered around Bumke's triad, and in many publications little attention is paid to any other phase of the status or reactions of the pupil. The observations here reported do not include any on this subject. In table 1 are summarized the more important pupillary symptoms of other kinds in dementia praecox. Of the reports considered, those of Reichmann and Knemeyer seem to be of unusual quality. Fuchs[12] presented a scholarly review of the literature to 1917 and expressed his own opinions.

The table adequately brings out the individual equation in the observation of the same phenomena. There is, however, a wide variation in the types of "dementia praecox" as well as many stages in the progress of the illness, and the variations shown in these figures by different observers depend not only on the individual interpretation of the various phenomena but also on the type of cases included. Rahne and Raecke included only catatonic patients. Some failed to state the types of dementia praecox, and others, although they specified the types, gave only the total figures. Consequently, these figures have questionable value except to point out that various pupillary anomalies are frequently seen in persons with dementia praecox.

RESULTS

Table 2 summarizes the data in the present series of 400 patients with deteriorated dementia praecox:

TABLE 2.—*Summary of Pupillary Anomalies in Four Hundred Patients with Deteriorated Dementia Praecox*

	No. of Cases	Percentage
Dilatation	71	17.7
Contraction	26	6.5
Inequality	44	11.0
Slight irregularity	92	23.0
Marked irregularity	24	6.0
Moderate light reflex impairment	107	26.7
Marked light reflex impairment	73	18.2
Impairment of convergence reflex	78	19.5
Absolute fixation	14	3.5
Argyll Robertson reaction	14	3.5
No anomaly	140	35.0

9. Meyer, E.: Pupillenstörungen bei Dementia praecox, Berl. klin. Wchnschr. **47**:1813, 1910.

10. Meyer, E.: Weiteres zu den Pupillenstörungen bei Dementia praecox, Neurol. Centralbl. **31**:1281, 1912.

11. Reichmann, F.: Ueber Pupillenstörungen bei Dementia praecox, Arch. f. Psychiat. **53**:302, 1914.

12. Fuchs, A.: Die diagnostische Bedeutung von Pupillenstörungen bei Dementia praecox, Psychiat.-Neurol. Wchnschr. **19**:127, 143 and 151, 1917-1918.

ANALYSIS OF ANOMALIES FOUND

Size of Pupil.—The percentages in this series agree in general with those of other observers in that the dilated pupil is much more frequently encountered than the contracted pupil. In this series, in the patients who were examined in a darkened room, pupils 2.5 mm. or smaller were classed as contracted, and those more than 5.5 mm. as dilated. This is an arbitrary division, although most writers have failed to define their classification of mydriasis and miosis. The percentage of cases in which dilatation was present (17.7) is higher than that of three previous observers but lower than that of three others. There is a remarkable uniformity for the figures as to the frequency of contracted pupils, varying only between 4.2 and 10 per cent, the present series showing 6.5 per cent. Weiler[7] found an average pupil width of 5.5 mm. in eighty-five cases compared with his series of normal persons showing 5.2 mm., although "average" figures in such instances are probably worthless.

Inequality.—This anomaly was present in 11.0 per cent. It was present in 7.5 per cent of the 1,000 general medical and surgical cases in the author's previous survey. Lewis[13] found 11.0 per cent in a series of normal persons, and Friberger[14] found that 44.6 per cent of normal persons show anisocoria. Consequently, it seems questionable whether it occurs any more frequently in persons with dementia praecox than in apparently normal persons. When one regards the significance of these figures, there are many factors to be considered: it is generally agreed that inequality may be hereditary (Wilbrand and Saenger,[15] Fuchs,[12] Piltz[16]); in the adult it is regarded by many as being always pathologic (Hansell and Sweet,[17] DeSchweinitz,[18] Fuchs[12]), and by others as physiologic in many cases (Barrie[19] Schmidt-Rimpler,[20] Fromaget and Fromaget,[21] Lewis,[13] Frith[22]). It is my opinion that its occurrence may be regarded as either physiologic or pathologic in schizophrenia, but its physiologic importance is nil and its pathologic importance seems to point to only a local regressive (degenerative?) change.

Irregularity in Contour.—For the purposes of classification, irregularity was divided into slight and marked, with 23.0 per cent showing slight and 6.0 per cent showing marked changes in contour—a total of 29 per cent showing some

13. Lewis, B. G.: In the American Encyclopedia and Dictionary of Ophthalmology, Chicago, Cleveland Press, 1919, vol. 14, p. 10603.

14. Friberger: Einige klinische Pupillenstudium, reference in Jahresb. u. d. Leistung. d. Ophth. **35**:218, 1904.

15. Wilbrand, H., and Saenger, A.: Die Neurologie des Auges, Munich and Wiesbaden, J. F. Bergmann, 1922, vol. 9, pp. 176, 245 and 254.

16. Piltz: Ueber die diagnostische Bedeutung unregelmässiger Pupillenkonturen im Verlaufe organischer Nervenkrankheiten, Jahresb. u. d. Leistung. d. Ophth. **33**:404, 1902.

17. Hansell, H. F.; Sweet, W. M., and others: Textbook of Diseases of the Eye for Students and Practitioners, Philadelphia, P. Blakiston's Son & Co., 1903, p. 452.

18. DeSchweinitz, G. E.: Diseases of the Eye, ed. 10, Philadelphia, W. B. Saunders Co., 1924, p. 65.

19. Barrie, T. S.: Inequality of Pupils, Brit. M. J. **2**:514 (Nov. 9) 1918.

20. Schmidt-Rimpler: Die Erkankungen des Auges im Zusammenhang mit anderen Krankheiten, Wien, 1898, p. 276.

21. Fromaget, C., and Fromaget, H.: Functional Anisocoria, Arch. d'ophth. vol. 36, p. 277; abstr. in Am. J. Ophth. **2**:356, 1919.

22. Frith, A. H.: The Pupil and Its Reflexes in Insanity, J. Ment. Sc. **60**: 82 and 224, 1914.

degree of irregularity. These figures are considerably higher than those in the series of general medical and surgical cases (13.3 per cent). The figures of other observers vary between 10 and 50 per cent. It was impossible in most of these cases to determine any history of previous disease or inflammation of the eyes, but patients with obvious iritis were eliminated from the series.

Light Reflex.—Of the total series, 50.9 per cent showed some disturbance of the reaction to light, a much higher figure than that in the general medical and surgical cases (13.4 per cent). Of this number, 26.7 per cent, or approximately a fourth of the entire group, showed a moderate impairment of the light reflex, either in the speed of the reaction or in the radius of the reaction arc. An additional 18.2 per cent showed a marked impairment in the light reaction, many of this group showing only a slight response to light. Fourteen cases (3.5 per cent) showed the typical Argyll Robertson reaction, and in fourteen additional cases the eyes were entirely fixed both to light and in convergence.

The group of patients with Argyll Robertson reaction might be materially enlarged if the persons showing marked impairment of the light reflex (not complete fixation) with only slight impairment of the convergence reflex were included. A fairly large percentage of those cases showing marked impairment of the light reflex would be included, since many of them showed less impairment of the convergence reflex than of the light reflex.

The coexistence of syphilis in these cases is possible but in most cases improbable. Three explanations may be offered for the Argyll Robertson reaction in the absence of positive serologic or other neurologic symptoms: (1) it may be the only remains of a healed or arrested syphilis; (2) it may be the isolated sign of a localized neurosyphilis; (3) it may be due to an organic disease of the central nervous system other than syphilis. When attention is called to the fact that these cases of dementia praecox are all of long duration, and in the absence of other unusual neurologic symptoms, with negative serologic symptoms, the first explanation is the only one of these three possibilities which might be applied. However, because of the relatively high frequency of the phenomenon (including the cases of absolute fixation) as well as the high percentage of cases showing impairment of the light reflex, not only of this series but of others recorded, such an explanation seems entirely inadequate. It seems probable that a fourth explanation must be suggested: this phenomenon may be due to organic regressive or degenerative change in the central nervous system. It is pure speculation to attempt to localize the site of this change, although several writers have suggested that it is a local change in the innervation of the iris.

Impairment of the Convergence Reflex.—In this series there was apparent impairment of the reflex in 19.5 per cent of the cases. Reichmann noted this in only three cases in her entire series. It is of special interest to record that in four cases of this series the convergence reflex was entirely absent, with the retention of some degree of the light reflex—the so-called paradoxic Argyll Robertson reaction mentioned by Kestermann,[23] Schwartz,[24] Levinsohn,[25] Bielschowsky[26] and others.

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23. Kestermann, G.: Beitrag zur akkommodativen Pupillenstarre ohne Lichtstarre, Klin. Monatsbl. f. Augenh. **70**:141, 1923.

24. Schwartz, O.: Zusatz zu vorstehender Arbeit über akkommodative Pupillenstarre ohne Lichtstarre, Klin. Monatsbl. f. Augenh. **70**:148, 1923.

25. Levinsohn, G.: Ueber einseitige Konvergenzstarre der Pupille, Klin. Monatsbl. f. Augenh. **70**:756, 1923.

26. Bielschowsky, H.: Konvergenzstarre der Pupillen, Klin. Monatsbl. f. Augenh. **71**:11, 1923.

COMMENT

The occurrence of approximately 30 per cent of the pupillary anomalies noted in general medical and surgical cases cannot be adequately explained either as congenital anomalies or as evidence of a physiologic (functional) or pathologic (organic) disease process. Similarly, 65 per cent of this series of persons with dementia praecox presented some pupillary anomaly for which there is no simple or well recognized pathologic explanation (neurosyphilis, localized inflammatory or neoplastic process, trauma, drug addiction, etc.). In the absence of the more unusual "silent" causes for isolated pupillary phenomena (healed or arrested syphilis, localized neurosyphilis with negative serologic symptoms, or organic disease of the central nervous system other than syphilis), further explanation must be found. The possible functional causes (as suggested by Bumke's triad) for the observed phenomena in such long standing cases seems inadequate. Similar anomalies are often seen in senility and are usually assumed to be degenerative changes. For these reasons, I have suggested that pupillary anomalies in the instances cited might be regarded as evidence of an inferior constitution or as stigmas of degenerative change.

The hypothesis of an inferior constitution in the patient with dementia praecox and the fact that the dementia is so often precocious might lead one to expect to find a certain degree of inhibition of further development, both physical and mental, before full development had been reached, which is subsequently followed by regressive changes. Along with other more delicate functions of the central nervous system, which are unquestionably impaired, one might conceive that a relatively sensitive organ like the eye would show some indication of change from the hypothetic normal as regards functional efficiency and anatomic structure.

In the various stages of different types of cases of dementia praecox when there is evidence from the patient's actions and speech of a tense psychic as well as perhaps a physical state, the pupils unquestionably show some anomalies which seem to be functional (i. e., on a physiologic rather than an organic basis) changes. It seems questionable, however, in the presence of a flattened emotional reaction, as seen in the hebephrenic type of dementia praecox in which the same response has been present for three, five, ten or even more years, that the pupillary changes could be interpreted on a purely physiologic (psychic) basis. It seems more probable that some organic lesion is present, though its site is speculative. It may be sclerosis or atrophy in the region of the synaptic connections in the nuclei, part of a diffuse change in the brain, or it may be due to local changes in the innervation of the iris.

SUMMARY

1. The pupils in 65 per cent of 400 cases of dementia praecox of long standing, which at the time of examination presented a hebephrenic type of reaction, showed some pupillary anomaly.

2. Dilatation occurred in 17.7 and contraction, in 6.5 per cent.

3. Inequality of the pupils was found in 11 per cent.

4. Slight irregularity occurred in 23 and marked irregularity in 6 per cent.

5. The light reflex was disturbed to some degree in 50.9 per cent, 26.7 per cent showing moderate impairment, 18.2 marked impairment, 3.5 fixation to light and retention of convergence reflex, and 3.5 per cent fixation to both light and convergence.

6. The convergence reaction was disturbed in 19.5 per cent, and in four cases was entirely absent with some degree of retention of the light reflex.

CONCLUSIONS

Pupillary anomalies, including irregularity, inequality and impairment of light and convergence reflexes, occur much more frequently in cases of dementia praecox, in which deterioration has occurred, than in general medical and surgical cases, excluding any relation to neurosyphilis in either group.

The relative frequency of the occurrence of pupillary anomalies in dementia praecox is inconstant, but the present study suggests their more frequent occurrence in cases in which deterioration has occurred than in the early cases reported by other writers.

In dementia praecox, as well as in approximately 30 per cent of general medical and surgical cases, pupillary anomalies do not bear a relation to any systemic disease and in these cases might represent either stigmas of regressive or degenerative change or inferior constitution. The high frequency of their occurrence in such a deteriorative illness, both physically and psychically, as dementia praecox (Kraepelin), lends strong evidence to such an interpretation.

CORRECTION

In the article, entitled "Neurinoma," by Dr. G. B. Hassin, Chicago (ARCH. NEUROL. & PSYCHIAT. **19**:1087 [June] 1928), the legends for figures 6 and 7, pages 1096 and 1097, should be transposed; the legend under figure 6 should appear under figure 7, and that under figure 7 should appear under figure 6.

MADAME DEJERINE-KLUMPKE

1859-1927

Obituaries

MADAME DEJERINE-KLUMPKE

1859-1927

To those who knew Professor and Madame Dejerine personally the passing of the latter marks the close of the life of one of the partners of a truly ideal marriage. I go back in memory some thirty years and recall an association which is almost as fresh as though it were of recent date. Professor and Madame Dejerine were hospitable to the stranger, and a glimpse of their home life on one of their charming Sunday evenings lingers in memory.

It was customary in those days for Professor Dejerine to arrive at the Salpêtrière about 10 a. m., and he was frequently accompanied by Madame Dejerine. She might visit the patients with him while he made his rounds or occupy herself in the laboratory in studying the large microscopic sections which formed the foundation of their magnificent work on the anatomy of the central nervous system. The identity of thought and purpose between husband and wife makes it impossible to separate the work of one from that of the other, and no one would desire to do so. To both, life meant labor in the advancement of the knowledge of medicine, and especially in that of the nervous system.

The gracious personality of Madame Dejerine stands out in bold relief. By an American this might have been attributed in part to a common bond of native country, for Madame Dejerine always recalled that she had been born in California and had spent her early life there. It seems fitting that her funeral should have been held in the American Church of Paris, and yet she could not have been more truly French. It would be a mistake, however, to fail to note that her personality was presented in the same traits to all who approached her. She was interested in any one who could speak her language of medical thought, and her quick mind readily grasped all that was said, and elaborated it.

The death of the husband in 1917 was a cruel blow to the wife, but she did not falter, and she carried on her medical work until the end. The beautiful eulogy recently pronounced by Professor Roussy before the Société de Neurologie has furnished much information regarding her life. No one was better fitted than he to write this tribute, because of his close association with both Professor and Madame Dejerine.

Madame Dejerine was one of the original members and was at one time President of the Société de Neurologie. Her entrance on a medical career was beset with difficulties which would have caused a less courageous spirit to quail. She encountered rebuff from some of those to

whom she was entitled to look for support, but her indomitable resolve caused her to become the first woman extern, and later intern, in the hospitals of Paris, and she led the way for others of her sex to follow. She made the acquaintance of Professor Dejerine early in her medical career, and their paths soon became closely entwined. Her paper, in 1883, on a form of brachial plexus palsy with ocular sympathetic palsy, quickly attracted attention and gave rise to the designation of Klumpke paralysis. It was followed by many other important studies, most of which were in collaboration with her husband. In later years, she had the comfort of the assistance of her daughter, who also was a former intern of the hospitals of Paris. Her later years were devoted to the establishment of the Dejerine Foundation consisting of a laboratory, library and neurologic museum which contain much of the work of husband and wife. She and her daughter, Madame Sorrel-Dejerine, established a fund for the support of original work in neurology.

A great personality has passed from the field of French neurology. Madame Dejerine rests by the side of her husband in Père Lachaise, and on their united graves may be read an epitaph which has been wisely chosen: "Labor et gloria vita fuit, mors requies."

WILLIAM G. SPILLER.

KARL PETRÉN
1868-1927

KARL PETRÉN

1868-1927

By Karl Petrén's death, Oct. 15, 1927, Swedish medicine lost one of its most prominent representatives. It may be said of him with reason that no Swede of the present day has had such a fruitful influence on the general development of medicine during the last few decades as he. There may be some who have been of more consequence in their particular branches of medicine and whose scientific contributions in their own province will prove of still greater value in the course of time. Still, Karl Petrén has excelled all by his versatility, his enormous energy and his indefatigable enthusiasm. Unquestionably, no other Swede has in like measure embraced within his activities and his interests so many different branches of medicine, practical as well as scientific. In his universality he stands supreme.

It is difficult to give in a few short lines a picture of this man of chieftain mold. His gifts made themselves felt at an early age. His fellow students tell of the attention he aroused during his school days by his comprehensive interests and his great alertness, by the energy with which he applied himself to his studies and, not least of all, by his fearless and sincere nature, qualities that have been characteristic of him during his whole life. In his student days he belonged to those circles at Lund University which attacked all questions relating to human weal and woe with fiery zeal. In this band of young iconoclasts Karl Petrén was at home, though the wisdom and stability that were the essence of his being saved him from excesses. It was during this period that Petrén's life received the idealistic bent that afterward laid its impress on his life work; it was then that there awoke that enthusiasm for knowledge and enlightenment as the best means of protection and progress for mankind, which made him such a zealous warrior in the fight against superstition and prejudice. It was also during his student years that birth was given to the great interest in human welfare that ever afterward was characteristic of him. He struggled disinterestedly all his life to attain this goal. It was this idealistic vein that came to the surface when, for instance, after the severance of the union between Norway and Sweden, he persisted in holding his position as Swedish member on the committee for the Scandinavian medical congresses. He often spoke of the pressure that was brought to bear on him, and of the personal unpleasantness to which he was subjected on account of his decision to remain on the committee. It is now known how fortunate it was that he did not abandon what he considered to be his duty and how successfully he assisted in the resumption of medical collaboration in Scandinavia. He manifested the same qualities during the World War,

when international collaboration among scientists was about to be completely broken off. Everywhere, with tongue and pen and by personal visits to the rival camps, he fearlessly and trenchantly laid down the postulate that research must be and must remain international. The personal esteem that he everywhere enjoyed gave weight to his representations, and his exhortations probably played no little part in the restoration of amicable relations between certain scientific societies of prominence. During the World War he found time in the middle of his strenuous work to pen a series of articles against certain outbreaks of chauvinism, which he regarded as one of the greatest enemies of mankind. Intrepidity and candor never failed to show themselves in him; they were integral parts of the charm that emanated from his person.

In his scientific productions, Karl Petrén dealt with most of the provinces of internal medicine. His young years were devoted principally to neurology. His investigations into the course of the sensory tracts in the spinal cord have been of fundamental importance. These works are quoted everywhere, testimony being given to their value most recently at the last Neurological Congress in Vienna, where sensibility was the chief theme. He often laid stress on the fact that in his scientific work he had never allowed himself to be led by what for the moment might be the modern view. He unflinchingly pursued his own paths and attacked the problems in the way intuition led him. Petrén won his first scientific success relating to the sensory tracts by a purely clinical method. This probably contributed to his giving, during his whole life, clinical observation the preference for the solution of physiologic problems in general. He invariably stated it to be his opinion that in reality clinical observation would pronounce the last word on such great problems as cerebral localization, aphasia and diabetes, to mention but a few instances. He remained in this way an enthusiastic worshipper of clinical observation. Petrén's results respecting the sensory tracts have been brilliantly confirmed by Brouwer of Amsterdam, who for many years has been carrying out thorough investigations into the question of the representation of sensibility in the central nervous system, and likewise by Bergmark. In conjunction with Bergmark, Petrén has written a work on the conditions of cutaneous sensation in zoster, and with Thorling, a work containing a critique of the ideas developed by Eppinger and Hess respecting vagotonia and sympathicotonia. The latter work contains, in fact, the modified view that is at present prevalent respecting these conditions.

During the years 1913 to 1919, Petrén took an active part on the commission appointed by the government to inquire into the occurrence of arsenic poisoning in dwellings. In this connection he undertook the task of working through the whole available literature on the subject, a task that he achieved with his usual thoroughness. As a consequence, he

reached the important result that under present conditions there is practically no danger of arsenic poisoning arising out of dwelling houses.

Petrén's most important contribution of late years has been made in the province of diabetes. During his stay at Naunyn's clinic in Strassburg, from 1897 to 1898, his interest was aroused in diabetes. After publishing, with Backman, a work on the factors contributing to the raising of the tolerance for carbohydrates in this disease, he began, after his call to the chair of practical medicine in Lund, to conduct a systematic investigation of the rich material provided by the patients with serious diabetes who passed through his hospital. This work culminated in his large monograph "Diabetesstudien" published by Gyldendal of Copenhagen, in 1913, and comprising 1,000 pages. The dietetic principles for the treatment of persons with diabetes developed in this work have everywhere attracted the greatest attention, and the term "Petrén's diet" is not uncommon in foreign handbooks on metabolic disorders.

As an author of textbooks, Petrén became especially prominent when, in the capacity of co-editor of the Scandinavian textbook on internal medicine, he undertook to write the chapter on neuropathic diseases. Many Swedish physicians testify that this account is entertaining and is presented with great skill. Space does not permit a detailed account of all the different medical works that issued from Petrén's pen. It must suffice to say that Petrén has left behind him an impressive legacy in his scientific writings, much of which will prove to be of permanent value.

It is natural that a man of Petrén's experience and ability should be called on for the most diverse tasks and duties. The interest he evinced during his time at Uppsala in the treatment of persons with tuberculosis resulted in his obtaining work on a committee appointed by the government for the arrangement of this matter; the lines he then laid down have since been determinative for the organization of this service. After he had returned to Lund, he became, as a matter of course, one of the leading spirits in the organization of sanatoriums in the county of Malmöhus. He assisted in the foundation of the well-known Orup Sanatorium and was president of its directorate. In 1912, at his instigation, the first tuberculosis dispensary in the county was erected. He also took an energetic part in the establishment at Lund of the institution for blind persons suffering from a complicated defect, and was also chairman of its board of management. The number of committees and boards on which Petrén effectively served was large. It was not in him to refuse whenever his services were requested.

Karl Petrén had a private practice of extensive proportions in Lund, in spite of the fact that the many journeys occasioned by his immensely diversified work made him inaccessible to his clients for long periods.

Petrén's love of traveling is to be regarded as an expression of his great intellectual activity. Even as a young man he set off on long journeys abroad in pursuit of learning. In 1896, he went to Paris, where he studied at Dejerine's clinic. The winter of 1897-1898 he spent with Naunyn in Strassburg. In 1905, he went to London, where he found Head and Horsley to be the chief representatives of English neurology. With these and other earlier foreign teachers, he never ceased to keep up cordial relations. Petrén was fond of visiting congresses. For many years no important scientific congress of his branch of medicine was held in Europe at which his tall form was not seen. He somehow found time for the congresses of the Central Powers as well as for those of the Entente. A few years before his death, he undertook a strenuous journey to the American clinics. So far he had only imperfectly mastered the English language. However, he learned this language rapidly and was able to take part freely in debates in America and England. Indeed, if an American or an Englishman happened to visit his clinic afterward, he would with perfect ease hold his ordinary lecture in the English language.

Abroad, Petrén was everywhere popular and had many devoted friends and admirers. He was looked up to as one of the chief representatives of Swedish medicine. The influence he had abroad on the reputation of Swedish medical science can scarcely be overrated. His recommendations have opened many foreign clinics and laboratories to young Swedish workers in science. Swedish scientists will always feel a debt of gratitude toward him for the manner in which he permanently maintained and cherished his foreign medical relations. There are probably few who throughout life have had such an enormous correspondence as Petrén. No one can have answered letters more promptly than he. At home he organized his correspondence practically, dictating his letters into a dictaphone at night. Even when on his travels he found time to write both many and long letters. Exemplary man of order that he was, he conscientiously collected all his letters, and this collection, which with the advance of time has attained considerable volume, will be of inestimable value for the illumination of medical development in Sweden and abroad during the last few decades.

As a ravenous searcher after truth, Petrén commenced at an early age to collect a library, to which he always devoted the greatest care and which, in course of time, attained enormous dimensions.

Few people have possessed such a capacity for work as Petrén. It may be said with reason that no one can have sinned more than he against the rule of hygiene that the hours of night should be devoted to rest. In spite of this he never appeared tired or burdened by his work. In most people a certain rhythm may be said to assert itself. Sometimes

they are more, sometimes less, disposed for work. In this respect, Petrén was invariably the same.

Of late years one has had the feeling that the great burden of work that Petrén shouldered was beginning to have some effect. He was as active as ever, though at times it seemed as if the grip he had on all his tasks was a touch less firm than before. It would, however, be incorrect to state that he was not still in the full vigor of manhood. He was full of energy and plans for the future. Just before his death he received the honor of an invitation from Barcelona to deliver lectures on his investigations relating to diabetes. This invitation pleased him greatly, and one of his last letters was an answer to his Spanish friends in which he promised to come.

To Petrén's sociability and benevolence, the assistants he had in the course of years can testify. Many have been struck by the cordial tone of good fellowship that prevailed between him and his subordinates. To all his young assistants he remained throughout the vicissitudes of life a fatherly friend, who as years rolled by continued to lavish his kindness on them. He was exacting in his work, but he placed still greater demands on himself. It is clear that a man who had to carry through a program of work on so many different subjects could not allow himself to be delayed by any hindrance to his daily work. He demanded above all precision from his assistants. Often he could develop an energy in the removal of an obstacle that to a bystander might appear as an expression of despotism. That is to be regarded as the recourse to which an energetic, conscientious man must sometimes have in order to get through his life work. Petrén was never resentful. His open nature was inaccessible to intrigue; he always fought with visor raised.

A man so richly endowed as Petrén, with his strong vitality, his optimism and his love of work, must have a highly stimulating effect on his associates, on his clinic and on his subordinates. There must not be any difficulties in the way of accomplishing a task. He himself knew none and was always ready with his tasks. The work at his clinic was based on the same general principles as far as his assistants could manage it. Petrén had a stimulating and inciting influence on the different classes of people with whom he came in contact; wherever he was known, and not least of all at his clinic, he leaves a great void behind him.

His death came unexpectedly while he was prosecuting his great work. As far as is known he had no presage of the disease that led to his death. Among his rich gifts was extraordinarily good health. For thirty years he had not been ill a single day, except for a severe concussion of the brain that he experienced about fifteen years before his death. On that occasion he lay unconscious for several hours. Otherwise, he had practically never been ill. When his temperature was taken the day before death, it was for the first time in thirty years.

Now that he has passed away so hastily it is only natural to think that his burden of work had been too heavy. If any one ever overworked the vessels of his brain year after year, it was Petrén. He was spared an awakening from the apoplectic stroke. To this extent, his mode of death may be regarded as a happy and beautiful one. He was able to dedicate his life to a great cause, and his consciousness was extinguished before he had begun to feel any decline, while he still stood at the height of his power. We who mourn him can only regret that he was wrenched from us so early. It is said that nobody is indispensable. One thing, however, is certain: for us who have reached mature years he will always be irreplaceable; we shall never again meet a man of his mold.

Peace to his memory.

SVEN INGVAR.

Abstracts from Current Literature

INDIVIDUAL ACQUIRED ACTIVITY OF THE CENTRAL NERVOUS SYSTEM. J. BERITOFF, J. f. Psychol. u. Neurol. **33**:113, 1927.

Beritoff, who is professor of physiology in the University of Tiflis and a disciple of Pawlow, presents in this paper the results of more than ten years' study on the fundamental nervous processes in the cerebral cortex, especially in its relation to the development of the so-called individual reflex. The paper is in German, and contains 335 pages and 73 illustrations. It is unusually rich in material, a knowledge of which is, in the abstracter's opinion, indispensable for the proper understanding of this phase of neurophysiology. It is manifestly impossible to abstract a paper of this size and to do full justice to the author's efforts and to the subject itself. This abstract, therefore, long as it is, consists merely of the author's conclusions on the various topics of the investigation; it is hoped that it will be sufficient to stimulate the reader's interest in this subject.

From his experiments, the author is convinced that individually acquired reflexes of the central nervous system cannot be distinguished from inborn reflexes. It has been well established that: (1) the former originate from the latter; (2) both may be produced by a stimulus from any peripheral receptive organ, and (3) their pathways run in the same nervous elements. Therefore, the laws of reflex action applicable to the inborn reflexes are of equal significance for the individually acquired reflexes.

The inborn reflexes have no stereotyped constant reactions and, under certain physiologic conditions, they may undergo changes similar to those of the individual reflexes. The latter are designated by Bechterew and his school as association reflexes. This designation, however, does not express their chief characteristic, so that Beritoff prefers to designate them as individually acquired or individual reflexes, because this designation carries with it the implication that they are just the opposite of the inborn reflexes. Following Levy's suggestion, the author calls an individual reflex elicited on the basis of another individual reflex, "an individual reflex of a higher order," whereas he applies the designation "secondary individual reflex" to one elicited secondarily by proprioceptive muscle, tendon and joint stimuli.

When an individual reflex is elicited for the first time after the application of a certain stimulus, such reflex will also be elicited after the application of other stimuli of the same kind, and occasionally also by another kind of a stimulus. This is known as the "generalization" of a reflex. Generalization of an individual reflex is never sudden. After some time the generalization of the reflex gradually disappears; it is then said to be "differentiated." When an individual reflex to an individual stimulus has reached complete differentiation and has formed a new reflex to the same individual stimulus by combining it with another active stimulus, the resulting differentiation remains at almost the same level. In this case the new formation of the reflex is by no means facilitated. The new reflex is generally developed after as many combinations as the original reflex. Any well differentiated reflex under certain definite conditions can be subjected to a new generalization — so-called "secondary generalization."

Types of Individual Reflexes.—A. Concurrent or Simultaneous Reflexes: An individual reflex appears soon after the beginning of the individual stimulus when the active stimulus follows by a few seconds the beginning of the individual stimulus. Such reflexes were designated by Pawlow as concurrent reflexes. The latent period of the individual salivary reaction in the concurring or simultaneous reflexes is usually a few seconds. The simultaneously observed swallowing reaction appears within about five seconds before the

salivary reaction, whereas the orientating reaction of the head appears much sooner, in about one second; the individual orientating reaction of the head also appears always sooner than the individual "movement" reaction of the feet.

B. Delayed Reflexes: Under certain conditions the individual reflex does not begin to appear at the beginning of the individual stimulus — not until from thirty to sixty or more seconds have elapsed. Such is the case when the active stimulus is not applied at the beginning of the individual stimulus, but from thirty to sixty or more seconds are allowed to elapse after the latter had begun to operate. This type of reflex is designated by Pawlow as a "delayed reflex." Under such conditions this type of reflex is not a delayed reflex from the beginning; it is at first a simultaneous reflex but as the latent period becomes gradually attached to the time point of the active stimulus it becomes a delayed reflex. These phenomena can be observed in the salivary reflex as well as in the formation of the protective "movement" reflex. Delayed reflexes may be as well differentiated as simultaneous reflexes.

C. Successive Reflexes: Under certain conditions the individual reflex does not appear during the application of the stimulus but some time thereafter. This is the case when the active stimulus is not applied while the individual stimulus is in operation, but one or two minutes later. This reflex corresponds to Pawlow's "Spurreflex" (vestige-reflex). Successive reflexes are usually not formed at the beginning. Although the active stimulus originates after the individual stimulus, the reflex is at the beginning a simultaneous reflex; later the individual reflex often appears during the duration of the stimulus and partly also after it. The successive reflex may also be developed at once, i. e., without a preceding simultaneous stage. The successive salivary reflexes are poorly differentiated, but ever so much better generalized and can readily become concurrent reflexes; they are not of long duration and can readily become extinct. Successive protective reflexes are of much longer duration and can be more frequently repeated than the successive salivary reflexes without combining the individual stimulus with the active one. The duration and stability of the successive reflex not only depends on the time interval between the individual stimulus and the active one but also on the duration of the individual stimulus. When the latter lasts only a few seconds and the interval also as much, the successive reflex is rapidly formed, stabilized and differentiated.

D. Negative Reflexes: Whenever an unusual stimulus is combined with the individual stimulus and this combination is not supported by the active stimulus, the individual reflex will appear either very feebly or not at all. Successive repetitions of this combination will be followed by a diminution of the negative effect of the unusual stimulus on the individual reflex. After a number of combinations the unusual stimulus ceases to have any effect on the reflex. Continuing these combinations still further the unusual stimulus begins, after a while, to act feebly on the reflex to make it finally disappear altogether. The negative effect is one of long duration.

E. Secondary Proprioceptive Reflexes: The individual movement reflexes are formed not only by stimuli from the external receptive organs but also by proprioceptive stimuli, i. e., by stimuli from the receptors of the muscles, tendons and joints, and, indeed, by those stimuli which are secondarily provoked while under the influence of the primary movement following an external individual stimulus or an active stimulus. That a proprioceptive stimulus may become an individual stimulus was shown long ago by Pawlow and Bechterew. Secondarily, reflexes not only condition entirely the after effects of the individual reflex, but to a considerable degree they also affect favorably, in a sense of intensification, the primary reflex to the primary individual stimulus. At the same time, it must be borne in mind that the secondary reflexes represent not only a reaction to a secondary excitation but also a reaction to a primary excitation, because the secondary reflexes always appear after the beginning of the primary excitation.

F. Rhythmic Reflexes: Under certain conditions the individual movement reflex runs its course rhythmically. The foot goes up and down several times; occasionally, the foot extends and flexes alternately, and almost in the same rhythm throughout the entire duration of the individual reflex. After the rhythmic reflex has been formed it can be elicited not only through the individual but also through the active stimulus.

G. Time Reflexes: This designation was originally applied by Pawlow to an individual salivary reflex following a repetition of the active stimulus — the feeding — in association with the individual stimulus, or even without the latter, after precisely measured intervals of time. After from 100 to 200 combinations the salivary reflex appears almost at the time of the active stimulus without any signal whatever. During the intervals the animal may occasionally fall asleep; this does not prevent the appearance of the reflex; on the contrary it may hasten it.

Variability of Individual Reflexes.—When an individual reflex has been repeatedly elicited, and this without a combination with the active stimulus, it becomes more feeble and vanishes or, according to Pawlow's terminology, it is "extinguished." During the extinction of a reflex there occurs not only a change in its intensity but also in its latent period, which becomes prolonged. The greater the duration of an individual reflex the more often must it be repeated in order to extinguish it. Feeble and recently acquired reflexes become extinct much sooner than old and more intense reflexes. Certain types of reflexes become extinguished sooner than others. The individual salivary reflexes disappear much sooner than the protective reflexes. Usually they disappear after ten repetitions. It is significant that not only the salivary reflexes but also the movement reflexes elicited during feeding disappear rapidly. The lowering of the intensity of an individual reflex during the process of its disappearance is extremely irregular; it occurs in waves precisely like the process of exhaustion of an inborn reflex. The individual reflex also becomes extinct after long interruptions. The feebler and more recent the reflex the sooner does it disappear after the interruption. Every individual reflex may disappear after one stimulation, provided the latter be kept up for a considerable period. An individual reflex may disappear by itself when any other homogeneous individual reflex is allowed to disappear. (Homogeneous reflexes are those formed by a combination with one and the same active stimulus; with one and the some kind of food, or with an electric stimulus to the same part of the skin.) This manifestation is designated by Pawlow as "secondary extinction." The more prolonged the extinguishing primary reflex is, the more thorough is the secondary extinction of the other reflex. There is, however, this difference between secondary and primary extinction: After a certain period of time secondary extinction is complete whereas primary extinction is only partial.

Relationship of Individual Reflexes to Foreign Unusual Stimuli.—Individual reflexes are sensitive to foreign stimuli. Every foreign stimulus weakens and may even abolish the individual reflex as soon as it appears as an unusual stimulus in the region in which the reflex in question was formed. In Pawlow's laboratory this phenomenon was found to have some relation to the animal's orientating reaction. A stimulus to which the animal has been unaccustomed weakens the reflex in proportion to the intensity of the animal's orientation reaction to that stimulus. On the other hand, an orientating reaction to every unusual stimulus becomes weaker and weaker as the latter is repeated, and finally the reaction disappears altogether. Corresponding to this, the negative effect of the unusual stimulus becomes weaker after the latter is repeated, and finally also disappears. The negative effect of unusual neighboring stimuli varies with the various types of stimuli. In dogs the orientating reaction to a sound stimulus is more intense and becomes less easily extinguished than the reaction to another stimulus. Some stimuli have longer after-effects than others. Sound stimuli exert a most intense physiologic effect, thermic and

gustatory stimuli the least effect, and mechanical cutaneous stimuli and some light stimuli have an intermediary position.

Fundamental Views as to the Origin and Changes of Individual Acquired Reflexes.—The Mechanism of Analyzers: An analyzer is a complex nervous mechanism with an origin in a receptive organ and a termination at the highest level of the central nervous system — the cerebral cortex. The receptive organ serves as a transformer of the corresponding external energy into a nerve process, whereas its cortical end is engaged in a complex process of analyzing the stimuli reaching it. Direct experiments have shown that the aural analyzer in the dog (analyzers are designated according to the particular end organ involved — aural, ocular, oral etc.,) is capable of differentiating the finest sounds and variations in tone. One of the most important properties of an analyzer, according to Pawlow, is the gradation of the analysis. A particular analyzer begins a temporary connection at first with a more general and coarser activity; with the continuation of its work and through the gradual differentiation going along with that its activity becomes finer and more precise. The cerebral cortex represents a combination of cerebral terminal ends of all analyzers. What is known as the motor center is nothing else than an analyzer which is associated or connected with the receptors of the motor organs; it is, therefore, designated as the movement analyzer. Every analyzer has a distinct and separate central area in the cortex where, as a result of its special structure, such as a thicker layer of cells, or richer association tracts, or owing to the absence of cells subserving other functions, there originate the most complex stimuli (higher synthesis) as well as their most precise differentiation (higher analysis). But the respective receptive elements (the analyzers) extend over very large areas, perhaps over the entire cortex; at the same time their position becomes less favorable the further away they are from the central areas. As a result of this, these stimuli become more and more elementary and the analysis more coarse. The experimental researches of Palladin, Babkin, Platonow and others on this phase of the problem have shown that the dog has an unusual capacity to synthesize a complex stimulus from simultaneous and successive components. It is this capacity for synthesis that is one of the basic functional attributes of the cerebral cortex.

The Development of Temporary Connections and the Generalization, Differentiation and Irradiation of Individual Reflexes: The existence in the cortex of foci of increased excitability and of reciprocity between them, due to stimuli exerting their effects simultaneously on them, determines the development of temporary connections. The initial point of the temporary connection is of little, if any, significance as far as the rapidity of its formation is concerned. This depends on the final point of the temporary connection in the sensorimotor apparatus. The reflex is obtained more readily and more easily the more the final point is prepared by previous activity, i. e., the higher its excitability and the more accurately it is localized. The generalization of an individual reflex to unusual stimuli depends, on the one hand, on the presence of cortical foci which are highly irritable on account of the action of repeated individualized stimuli in combination with electric stimuli, and, on the other hand, on a generally increased irritability of the entire cerebral cortex; it is on the latter that generalization depends during the development of the individual reflex, as well as when it occurs later. During the period of generalization unusual stimuli differing markedly from the usual one give rise to the usual reflexes on account of a direct irradiation of the excitation into the cortical center representing the final point of the developing temporary connection. Unusual stimuli, more closely allied to each other, give rise to a reflex through temporary connections, owing to the irradiation of the excitation into the cortical focus of the individual stimulus, which is the initial point of the temporary connection. Differentiation of an individual reflex depends on the gradual diminution of the irritability of the cortex outside the reciprocally acting foci. This is brought about by the temporary connections being associated with an increase of the irradiation of the excitation into the pathways

of the temporary connections, and into some inborn pathways that lead from the sensory area to the motor apparatus. Owing to diminution of the excitability in the cortex, unusual stimuli fail to give rise to a reflex because the feeble excitations that they evoke in the cortex are unable to affect by irradiation the local irritable foci, i. e., the initial and final points of the temporary connection. The irradiation of an excitation through the cerebral cortex proceeds on the principle that the more it irradiates into highly excitable pathways the less will it irradiate into less excitable pathways. This is known as "interdependent irradiation" and is not peculiar to the cerebral cortex alone but may also occur in the irradiation of spinal excitations.

The Cortical Elements of the Reflex Arc of Individual Reflexes: The cortical component of the reflex arc of an individual reflex consists of: (*a*) the cortical focus which is the receptor of the individual stimulus; (*b*) the sensory cortex which is stimulated by the electric stimulus (in the case of the olfactory cortex the part stimulated by the stimulus of the oral cavity); (*c*) the cortical areas which are the receptors of the secondary proprioceptive muscle, tendon and joint stimuli; (*d*) motor centers for the limb which are in intimate inborn connection with the corresponding proprioceptive cortex and the sensory cortex, and (*e*) numerous connections between these elements of the cortex, constituting temporary paths of various complexity. Numerous secondary reflexes are superadded to the primary individual reflex excited by an individual stimulus, owing to the establishment of special temporary connections between the cutaneous analyzer and motor apparatus excited in the primary reflex, and the part of the motor analyzer excited by secondary (proprioceptive) stimuli from the tendons, muscles and joints. In primary as well as in secondary reflexes the activity of complex temporary pathways with a cutaneous analyzer is shown by general movements and sound reactions, while the activity of simple temporary pathways without a cutaneous analyzer manifests itself by isolated movements of the limb. On the strengthening of the individual reflex the complete temporary pathways of both primary and secondary reflexes become less excitable and active, owing to the greater development of temporary connections in the simple than in the complex pathways. The formation of temporary connections is in mammals a cortical function; they are formed exclusively between elements of the cortex but not between these and any other noncortical elements. All connections between both of these kinds of elements must be innate. In lower vertebrates as well as in birds, temporary connections may also be formed in the subcortical nuclei (striatum and thalamus). In these animals, individual activity is also retained after ablation of the cerebral cortex.

Extinction of Individual Reflexes: There is nothing specific about the peculiarities of exhaustion of the positive individual reflex during successive rapid repetition during prolonged activity. The mode of exhaustion is the same in the inborn noncortical activities of the central nervous system as in the individual reflexes. The extinction of the individual as well as of the innate noncortical reflexes depends on exhaustion of the central nervous system; it is conditioned on the one hand by exhaustion of the mechanism of the progressive temporary connections, and on the other, by exhaustion of their terminal points in the areas for movement and secretion. The sequelae of exhaustion of the terminal points, i. e., the diminution of their excitability and functional activity, is transitory, a characteristic of all components of the spinal reflex arc. The sequel of exhaustion of the mechanism of the progressive temporary connections is also transitory when the extinction of the reflex took place only once. But during deep and repeated extinction the sequelae of exhaustion of the temporary connections is not complete after one period of rest, because through the process of exhaustion the mechanism of temporary connections is itself disturbed to such an extent that rest does not restore it to its previous functional capacity. In addition to this there occurs during the period of deep exhaustion a marked development of the regressive connections, because the focus of the individual stimulus offers unusually favorable conditions as far as increasing the excitability is concerned. The primary

single extinction of an individual reflex, which disappears after a period, depends simply on the exhaustion of the progressive temporary connections and their terminal points, but the complete permanent exhaustion depends chiefly on the disturbance in the mechanism of the progressive connections, and, to some extent, on the marked development of the regressive connections. The secondary disappearing extinction of the homogeneous reflex after a period of rest is chiefly conditioned by the exhaustion of the reciprocal terminal points of the temporary connections, whereas the secondary protracted extinction of such a reflex depends chiefly on the negative effect of the regressive connections of the temporarily extinguished reflex on the activity of these points.

Restitution of Individual Reflexes: The delayed revival of an extinguished reflex after a preceding electric stimulus or following the elicitation of another homogeneous reflex depends on the increase in excitability in the cortical terminal points and also in the other elements of the temporary connections, but not on the reestablishment of the latter. A more or less complete restitution of an extinguished reflex following a period of rest occurs only when the extinction has not been complete. It depends, above all, on a recovery of the progressive temporary connections. In the case of a deep, repeated extinction the disturbance of the progressive temporary connections becomes so great that even after recovery, i. e., after the exhaustion has ceased, they still remain disturbed. An actual restoration of a more or less completely extinguished reflex occurs only when a combination with the active stimulus has taken place, and this again is similar to the new formation of a reflex. The restoration depends on the removal of the disturbances of the progressive temporary connections which has been brought about by the activity of the reflex in one direction, and not on the removal of the exhaustion. In other words, it depends on an increase in the morphologic and functional development of the progressive temporary connections, thus resembling completely the new formation of an individual reflex.

The Relation of Individual to Other Reflexes.—The relation of an individual stimulus to an individual reflex provoked by another individual stimulus is an extremely variable one. The individual stimulus usually exerts a positive effect on another homogeneous reflex, which becomes somewhat more intense or remains wholly unaltered. Every one of the combining stimuli produces an increase in the excitability of the entire cortex; this is due to an irradiation of the excitability of all active cortical elements. Nevertheless, owing to the fact that both reflexes have a common terminal point of the temporary connections there occurs by virtue of the augmentation of the peripheral effect and of the simultaneous action of both stimuli a rise in the excitability of the terminal point, because the latter is affected by the temporary connections of both reflexes. Only in the case of an extinction of a reflex which led to an exhaustion of this common point can the extinguished reflex have a negative effect on the other homogeneous reflex. The relationship between the various reflexes to each other is conditioned chiefly by their duration and intensity. One of longest duration and greatest intensity eliminates a comparatively feeble reflex. When the combining various reflexes are feeble and insufficient in duration, both reflexes may disappear during a combination of the respective individual stimuli. The relationship of the individual successive and delayed reflexes to the simultaneous ones is practically identical with that of the simultaneous reflexes. A negative individual stimulus has a negative effect not only on a definitely positive reflex with which it was combined to produce a negative reflex but also on any other homogeneous positive reflex. A negative individual stimulus can also have a negative effect on a heterogeneous positive reflex when the temporary connections have not yet become strongly united. Under these conditions the negative stimulus can produce a marked rise in the excitability and enhance the dispersion of the latter from the temporary connections. In the presence of a foreign stimulus the negative stimulus ceases to have a negative effect on the positive individual reflex. This is the case in which the foreign stimulus is one of feeble physiologic effect, and when the excitations

from the relatively weakly formed temporary connections of the negative reflex are more dispersed than those from the cortical elements of the positive reflex. As a result of this, the excitability of the regressive connections is not raised to the same degree as that of the temporary connections of the positive reflex into which that of the negative reflex extends. An innate reflex may also have a negative effect on an individual reflex. This must be conditioned on the one hand, by the generally increased excitability in the cortex, and on the other, by the inhibition of the individual peripheral effect under the influence of the antagonistic reciprocal innervations from the coordination apparatus of the innate reflex.

The Effect of Some Physiologic States on Individual Reflexes.—Any change in the irritability of the central nervous system has a definite influence on individual reflexes: increased irritability gives rise to an increased intensity of the reflex, its generalization, slight delay or a conversion of a delayed reflex into a concurrent reflex. This is observed in cases of poisoning with caffeine and other measures which increase excitability in general, in cases of mild starvation and in states of mild physical exhaustion. In cases, however, in which the excitability of the central nervous system is subnormal the reflex is inconstant, more readily extinguished and better differentiated. This occurs when the organism is under the influence of such drugs as sodium bromide. When on the other hand, the physiologic state is such that the irritability of the central nervous system is still more depressed — as during exhaustion following prolonged starvation — the formation of an individual reflex, and with that its differentiation, becomes very difficult. In cases of more advanced depression, such as agonal states following starvation, the irritability of the central nervous system falls to such a low ebb that individual activity ceases altogether.

KESCHNER, New York.

THE ETIOLOGY OF VASCULAR NEUROSIS AND SOME FORMS OF PAIN. MICHAEL LAPINSKY, Ztschr. f. d. ges. Neurol. u. Psychiat. **106**:171 (Dec.) 1926.

Lapinsky applies the name vascular neurosis to conditions, without known organic cause, which produce either a dilatation or a constriction of the vessels. He reports a case in a man, aged 40. The contractility of the peripheral capillaries is of great importance. They form the blood reservoir on which the turgor vitalis, regulation of body warmth and nourishment depends. The contractility of an organ is dependent on the amount of contractile elements present; the capillary walls are lacking in such elements. The smallest capillaries possess only a vessel membrane (the endothelial intima). In the arterioles there is also an adventitia, but neither adventitia nor intima contain contractile elements. Di Gaspazo is convinced that capillaries contract. Worms and Müller postulate contractility of the capillaries in regulation of the blood pressure. Richet explains a palsy and anesthesia in the arm on the basis of an isolated capillary spasm. Tonita observed contraction of capillaries when they were subjected to oxygen, and dilatation when they were subjected to carbon dioxide. In a case of Raynaud's disease, Nickan was unable to find capillaries with a skin microscope. He concluded that they were in a state of spasm. Parissins is convinced that capillaries can contract and dilate under the influence of nerves. He, too, used a skin microscope and made observations similar to those of Nickan. Sigmund Mayer found, in the intestinal capillaries of the salamander, occasional cells of peculiar form which he numbered among smooth muscle. He saw similar cells in the sclera of the eyes of frogs. Steinach and Kahn postulate that these cells play an active rôle in the constriction of capillaries. They stimulated, with an electric current, the membrana nictitans of a frog and the omentum of a guinea-pig or cat, and produced narrowing and obliteration of the capillaries. Marchand looks on the so-called muscle cells, on which Steinach and Kahn base their theory, as merely aberrant intimal cells

which have nothing to do with the muscular system. Rosenthal and Wyssoxovitch found similar cells in the liver and ascribe to them a phagocytic function.

Other observers throw doubt on the constriction of capillaries by experimental means. The Weber brothers could not demonstrate any constriction by electrical stimulation. This was confirmed by Gunning and Donders who could not find any constriction of the capillaries in the skin of the frog after stimulation of the ischiadic nerve. Jacob found capillary constriction apparent under the influence of phenobarbital, but said that this was not an active constriction, but a passive collapse of the vessels. Others, similarly, deny the ability of the capillaries to contract actively, and state that the narrowing is a passive rather than an active process. Auer, Biol, Baloch and others are of this opinion. Lapinsky states definitely that an active constriction of the capillaries has not yet been observed. In man, the capillaries play a passive rôle in the circulation of the blood. Their width depends on the tonus of the surrounding tissues, but to even greater degree on the contractility and caliber of the arteries which conduct the blood to them.

The medium sized arteries such as the brachial, radial, ulnar and other arteries, possess smooth muscle coats, but they play only a moderate rôle in the vasomotor sphere; little is known of their constriction by electrical stimulation, except in the case of the renal vessels which may lose their lumens as a result of such irritation.

The vasomotor centers for the upper extremities are in the thoracic cord chiefly at the segments from the fifth to the ninth dorsal but spread as high as the third and as low as the eleventh. The fibers leave the cord by the anterior roots, go to the stellate ganglion and enter the brachial plexus by the rami communicantes. Their distribution in the upper extremities is in accordance with metameric arrangement (Bayliss, Langley, and others). The vasomotor centers for the lower extremities are in the lower thoracic and upper lumbar segments. All these centers are metamerically arranged in the spinal cord and can activate vessels in definite segments on excitation. They can be excited reflexly by hormones and other chemical agents. Many investigators have attacked the problem of the origin of this excitation or stimulation. Hallion and Compte, by means of a plethysmograph, recorded narrowing of the peripheral vessels on stimulation of the mucosa of the intestine or lung. Mackenzie and many others believe that the peripheral vessels are directly under the control of the visceral organs and nerves. Cantru, Romano and Hallion-Frank observed dilatation of the peripheral vessels on kneading the intestines of a dog. These and other observations lead to the conclusion that the peripheral vessels can dilate or contract in a purely reflex manner by stimulation of the internal organs. Lapinsky believes that both these phases, dilatation and contraction, are expressions of activity of vasoconstrictor centers, short stimuli causing vasoconstriction and larger stimuli producing vasodilatation by fatigue of the vasculature. Many clinical observations bear out the relation of the lumen of the vessels to the inner organs. Quincke asserts that in an attack of gallbladder colic the pulse is small and the skin blanched. At the time of the passage of the stone, the extremities are cold and the pulse is very small. Botkin has noticed that diseases of the liver may be evidenced by vascular disturbances without the presence of complaints in relation to the liver; he notes observations similar to those of Quincke in the passage of a gallstone. In some cases the stimulation of liver processes is accompanied by a subnormal temperature only on one side—the right—and the right pulse is found to be smaller than the left. Botkin has noticed definite variation in the lumens of vessels at the time of passage of a gallstone—at first dilated, then contracted, and again dilated. He has noted a dilatation or constriction of vessels far removed from the original focus of stimulation when the stimulus is maintained for a long time. Smianowsky, in an experiment on a dog with a fistula of the gallbladder, stimulated the mucosa of the gallbladder and observed significant vascular changes—the right crural artery was constricted

and its pulse hardly palpable while the left was full. The temperature in the right and left axillae was different.

Lapinsky reports several cases of what he calls vascular neurosis in which there were definite vasomotor disturbances in the body as a result of disease of the viscera.

CASE 1.—A man, aged 50, had definite enlargement of the liver and complained of pains in the sternum and legs with feelings of coldness in the extremities. He had several attacks of gallbladder colic and after one of these attacks showed definite vasoconstriction in the left femoral artery distribution and in the right lower extremity, together with pains in these areas.

CASE 2.—A young woman complained of pains in both hands and feet and coldness in all extremities, which condition had come on after an attack of appendicitis with abscess and peritonitis. There were coldness, cyanosis, and pains in the extremities. The stimulus in this case was the inflammatory condition of the viscera which affected especially the thoracic cord as shown by the absent abdominal reflexes and the cramplike condition of the peripheral vessels. Lapinsky believes there can be no doubt of the visceral origin of the peripheral vasoconstriction because of the fact that the latter disappeared after the application of heat to the abdomen for four months.

CASE 3.—A man, aged 40, had a constriction of the crural artery as the result of pelvic irritation, disease of the spermatic cord.

CASE 4.—The patient had brachial neuralgia and a prolonged cramp of the brachial artery as a result of disease of the sexual organs.

Lapinsky also, by means of several cases, calls attention to certain obscure cases of pain and paresthesias in the extremities and other peripheral parts as a result of disease of the viscera. He cites two cases of pain and acrocyanosis as a result of irritation in the pelvis. These were in the lower extremities. He has also seen evidences of vascular spasm in the upper extremities as a result of disease of the stomach and liver. He says there are probably hundreds of similar cases of paresthesias and pains as a result of irritation of internal organs, and that clearing up these foci would cure them.

These conditions do not occur only in the extremities, but also in the trunk, and especially in the breast and abdomen. In some cases of appendicitis, dermographia in the abdominal wall is lacking or weak and the color of the skin over the abdomen is pale. With the removal of the pain these again become normal. In many cases these signs are symmetrical, but in others they are not, as in diseases of the pelvis, cecum and ascending colon. Wericoe, on the other hand, has observed symmetrical anemia over the breast and abdomen in a disease of the intestine which was unilateral. This is hard to explain. Experimentally, it has been shown that vasomotor centers on one side of the cord govern both sides of the body. Nikolaides was convinced that on stimulation of a vasomotor center there occurred bilateral phenomena. He observed this after longitudinal section of the cord and after stimulation of either side.

The mechanism of these vascular and pain symptoms is the same in all cases. There is first an excitation of one or several organs. The stimuli flow through the nucleus sensorius proprius of the posterior horn to the vasomotor centers of the first order in the cord; they may be strong or weak. In the first case a refractory stage is set up in the nucleus sensorius proprius and many stimuli, therefore, do not reach the vasomotor center, so that they remain inactive and the vessels under their control dilate. In the second case, weak stimuli, reach the spinal centers and cause a stimulation of the peripheral vessels with subsequent constriction. In the first case a hyperemia — erythema or acrocyanosis — appears, while in the second, acroasphyxia or acroparesthesia occurs. In this way peripheral vascular phenomena can be conceived of as reflex events, the excitor of the reflex phenomena lying in the disturbance of the visceral organs.

ALPERS, Philadelphia.

CONTRIBUTION TO THE STUDY OF MIND-BLINDNESS. ADOLPH HEIDENHAIN, Monatschr. f. Psychiat. u. Neurol. **66**:61 (Oct.) 1927.

The author reports an unusually clearcut and uncomplicated case of partial mind blindness. The patient, aged 45, suffered from myocarditis with symptoms which dated back to 1921. In 1925, he had a stroke of paralysis, resulting in an inability to read. Recognition of pictures was somewhat difficult, but possible. There was not any difficulty in speech or movement. Three months later there was a second stroke. Following this he could still see, but "could not understand" what he saw. Visual acuity was reduced to one-fifth. There was a right-sided hemianopic defect in the upper quadrants. There was a marked disturbance of color vision. In addition to these visual defects, there was a definite gnostic disturbance. He could find his way about the streets that he knew well, but not in any strange places. He was unable to recognize people, even old friends. He could tell nothing about the food on his plate, except by smell and taste. The patient himself recognized the difficulty, and said he could see well enough, but "couldn't understand things he saw." Recognition of objects was difficult. He followed the contours of the object, recognized differences in size, shading and configuration, but with all these details he might fail, or else, largely by the trial and error method, arrive at a correct solution. In drawing, he did surprisingly well, even though not recognizing the object he was drawing. The same was true for copying writing, which he was wholly unable to read.

Older authors, in attempting to explain mind blindness, have considered it due to loss of optic memory pictures or to a break in the association tract between the end station of the optic radiation and the cortical zone which holds the optic memory pictures, or perhaps between the optic radiation and the memory pictures of other sense zones necessary for concept formation.

The author recognizes the difficulty of determining how clear the optic memory pictures are, but he feels that in this case, at least, they are not lost. For example the patient describes a thirty minute walk from his house to the clinic with absolute accuracy; and he can find his way alone. At the same time the memory pictures are not normal; for example, he often finds it hard to give the color of an object from memory.

A study of reading is interesting. By testing the patient with different types of letters, large and small, German and Latin script, he found:

		Latin Script		German Script	
	Figures, Per Cent	Large, Per Cent	Small, Per Cent	Small, Per Cent	Large, Per Cent
Correct	100	70-75	45-50	30-50	0-32

The figures were all read correctly. The Latin capitals were read right in from 70 to 75 per cent of the cases; the German script capitals in from 0 to 32 per cent. This must mean that the ability to read letters depends on the optic structure of the letter, the ease of recognition being inversely proportional to the complexity of the letter—the simpler and clearer the structure, the readier the recognition. There is no defect in naming the letters, once they are recognized.

The ordinary association theory explanation of alexia does not explain this. The basic principles of the association theory have nothing to do with complexity or simplicity of the structure. The fixity of the association is dependent on the intensity of attention and the frequency with which that association is made. This weakness of the theory has been recognized before; it has been hard to explain why these patients read numbers more easily than letters. Some elaborate adaptations of the association theory have been arranged to explain this, but they are not adequate.

In studying the patient's reactions, when he is attempting to sort out groups of letters, placing together those of one kind, the author found that the patient does not study the letter as a whole, but divides it into parts, studies each

part separately, and compares it with corresponding parts of other letters to determine like and unlike. The grasp of the letter as a whole is grossly disturbed; he cannot retain it in memory long enough to compare it with other letters; so he takes it part by part.

The alexia which the author's patient showed was proportional to the balance of his mind blindness, so the same mechanism which obtained for reading probably obtained for the recognition of objects in general. The disturbance is one of grasp of the object as a whole. As for letters, so for drawings or pictures — the patient takes them apart, gets a suggestion here and another there and, finally, builds together a whole which is partly reasoned, partly guessed and all trial and error. One gets the impression that the inability to reach a correct appreciation of the object as a whole is due to inability to build the various partial meanings together, rather than to a pure disturbance of the visual picture.

As stated, the author is not satisfied with the older association theory — that mind-blindness is due to a break between the optic end stations and the zone of optic memory pictures. He finds more satisfaction in the theory formulated by Pick and elaborated by Goldstein. They described two types of mind-blindness. In one, as in a case described by Goldstein and Gelb, "the optic recognition of the patient was grossly disturbed in such a way that characteristic optic impressions were not produced, although the elements were there." This patient could not recognize the simplest figures — a straight line or a crooked line. And the loss of such characteristic form impressions was the cause of the alexia and mind-blindness. They spoke of this as a total form blindness, or in the old Lissauer terminology, an apperceptive mind-blindness. The other type, classed according to the Lissauer terminology as an associative mind-blindness, is that in which the patient can grasp optically the structural peculiarities of objects; but the object, of which an adequate picture is formed, does not have any meaning. It cannot be named and its use cannot be recognized. It is to this group that the author's case belongs. Between the two groups there does not seem to be any connection.

Pathologically, there was a lesion in both occipital lobes, almost symmetrical. It involved the basal surface of the occipital lobes, the gyrus lingualis, gyrus fusiformis and the third occipital lobe. The occipital pole on the left was relatively intact, and on the right, almost gone. The major part of the calcarine lies outside the lesion.

This confirms Nothnagel's view that marked mind-blindness is almost always due to bilateral lesions (or to a left-sided lesion with additional involvement in the splenium).

The time relation of the two lesions is clear. The left-sided lesion came first and produced an alexia. Then came the right-sided lesion and converted the alexia into an outspoken optic agnosia. It is interesting that the alexia was caused by a lesion of the left occipital lobe and not by a lesion of the angular gyrus. Some authors deny the relation of the angular gyrus to alexia. It may be, however, that both lesions may produce an alexia of different type, the occipital lobe type impairing chiefly the recognition of the optical structure of letters, the angular gyrus an alexia not dependent on purely optic factors.

SELLING, Portland, Ore.

PATHOLOGY OF FATAL CEREBRAL EDEMA: A CONTRIBUTION TO THE STUDY OF REMOTE EFFECTS OF BRAIN TUMOR. ERWIN STENGEL, Jahrb. f. Psychiat. u. Neurol. **45**:187, 1927.

A woman, aged 53, presented an exquisite cerebellar syndrome on the right side of the body with general symptoms of tumor of the brain. The clinical picture was that of a tumor in the right cerebellum. The presence of slight pyramidal tract symptoms was attributed to pressure on the contralateral pyramidal tract. Necropsy revealed a normal cerebellum and a small tumor in the white substance of the left occipital pole. The course of the disease was

characterized by repeated attacks of prostration and vomiting, i. e., acute cerebral compression which had eventually led to an epileptiform attack. On section, the cerebral edema was striking, especially because it was limited to only two parts of the brain: the entire left cerebral hemisphere and the mesencephalon. Secondary edema of a hemisphere due to tumor is common and leads frequently to errors in diagnosis. The unusual features in this case were the localized edema and hemorrhages in the mesencephalon. This local process can be explained only on the theory of pressure by the swollen left cerebral hemisphere. The fact that a unilateral swelling of a hemisphere had such a remote effect on the localization of the tumor is not only of anatomopathologic, but also of clinical interest.

There can be doubt that the cerebellar symptoms were due to involvement of the cerebellar tracts in the mesencephalon by edema in that structure. The cerebellum itself being intact the cerebellar symptoms could not be attributed to tumor directly. There was not a single symptom referable to the site of the tumor, so that one could actually speak of a "pseudotumor cerebri" in a case of tumor cerebri. Pathologic examination also did not leave any doubt that the cerebellar symptoms could not be due to involvement of the temporal lobe. Türck's bundle was found intact. Nor can it be maintained that the ataxic symptoms were due to a lesion of the occipitopontile tracts. As far as the author could gather there is no case on record in which a lesion of the occipitopontile tracts gave rise to cerebellar symptoms, unless there was in addition to that lesion also swelling with secondary pressure on the cerebellum. The question then arises what was the mechanism of the symptomatology in the case. The simplest explanation would be that as the result of the swelling pressure was exerted on the cerebellum which was in turn transmitted to the mesencephalon. This, according to Redlich, is the usual way in which pressure effects of occipital processes produce cerebellar symptoms. The cerebellar hemispheres in this case showed only moderate flattening of the convolutions. Furthermore, the cerebellar symptoms were predominatingly on the right side whereas the tumor was in the left occipital lobe, so that if they were due to direct pressure they should have been on the left side. It is therefore certain that direct pressure effects played only a subordinate rôle. The most reasonable explanation would then be that the swollen cerebral hemisphere exerted its pressure effects on the anterosuperior portion of the mesencephalon from left to right, interfering with the conductivity of the cerebellar tracts reaching the right side of the mesencephalon. The deformity and compression of the posterior part of the corpus callosum toward the right would seem to be corroborative evidence in favor of this hypothesis.

The cause of the fatal cerebral edema was a relatively small, completely isolated metastatic carcinoma whose primary focus could not be found at necropsy, and did not give clinical symptoms during life. Sternberg, who examined the tumor sections, thought that the metastasis was most likely from a bronchial carcinoma, which is so frequently overlooked at necropsy and which also metastasizes unusually early.

The swelling of the mesencephalon was in the nature of a true edema. The case belongs to the group of cerebral swelling with negative histologic observations in the swollen tissues immediately adjacent to the tumor. The increase in volume could not be attributed to ameboid gliosis. The choroid plexus did not show sclerosis or proliferation to account for any abnormal secretion in Pilcz's sense. The swollen hemispheres did no show evidences of hemorrhage nor even of hyperemia. Clinically, the first attacks of cerebral edema appeared about two months before death. It may be that it was then that the metastasis had first made its appearance, although the presence of many corpora amylacea, especially in the ventricular wall, would seem to be in favor of a more chronic process. In addition to the marked swelling, the mesencephalon also showed evidences of numerous "diapedesis" hemorrhages; the histologic appearance of these pointed to their origin during the later and most violent attacks of edema. The hemorrhages were especia'ly intense in the region of the locus coeruleus.

According to Hess and Pollack, lesions in this region give rise to disturbances in breathing and these observers are inclined to regard this nucleus as a respiratory center. In view of this it is significant that the patient in this case suffered from unusually severe respiratory disturbances during her last hours—a period corresponding chronologically with the onset of the hemorrhages in the locus coeruleus.

The presence of so many hemorrhages in the mesencephalon is also interesting from another point of view. It is well known that in some pathologic processes affecting the entire central nervous system the vascular changes are most marked in or are even limited to the midbrain; this is especially the case in intoxications. In the case reported the pressure effects, although generalized, found greatest expression in the mesencephalon as evidenced by the preponderance of edema and hemorrhages in this structure. Apparently of all the cerebral vessels affected by the pathologic process those of the mesencephalon constitute a locus minoris resistentiae and are especially vulnerable. This is analogous to the selective involvement of certain definite parts of the brain (pallidum, cornu Ammonis) in the course of some infections and intoxications.

The chronic ependymal changes pointed to the chronicity of the mesencephalic involvement which must be postulated in order to be able to attribute the cerebellar symptoms to the changes in the mesencephalon. Although there was not the slightest evidence of inflammation in the sylvian aqueduct, the ependymal cells showed such marked proliferation that the histologic picture was typical of an ependymitis granularis. Some areas also showed evidences of a marked defense reaction of the subependymal glia. The glial wall was so well formed that it lent additional corroborative evidence that the lesions in the mesencephalon were not of recent origin and that they must be regarded as the pathologic basis of the symptomatology in the case.

KESCHNER, New York

THE SIGNIFICANCE OF THE VERMIS OF THE CERERELLUM FOR SUGAR REGULATION. TETSUSHIRO SHINOSAKI, Ztschr. f. d. ges. Neurol. u. Psychiat. **106**:483 (Dec.) 1926.

Since Weichselbaum it has been thought that the majority of cases of diabetes are due to disease of the pancreas, although the existence of diabetes due to disease of the nervous system was known to Claude Bernard. Since the discovery of insulin it has become apparent that there cannot be diabetes without disease of the pancreas; this is supported by definite pathologic observations. On the other hand, Nakamura asserts that in infants atrophy of the pancreatic island does not represent a specific change in diabetes, because in children of that age who have died of a generalized atrophy or an acute toxic process without an increase in the blood sugar, there is often a complete or partial atrophy of the islands of Langerhans. It is well known also that irritative or destructive lesions of the hypothalamus cause hyperglycemia. Of particular significance in this connection are the nuclei periventricularis in the midbrain and the vagosympathetic nuclei of the medulla (Camus, Müller and others). The nervous types of diabetes which occur without changes in the pancreas are ascribed to these loci.

Shinosaki reports the case of an infant, aged 4 months, with normal birth, who showed marked pallor, atrophy and adenopathy on examination. There was 2.4 per cent of sugar in the urine. The sugar content varied from day to day from 0 to 9 per cent in spite of a constant carbohydrate intake of 145 Gm. After twelve weeks, acetone appeared, but reduction of the diet produced good results. The patient died with bronchopneumonia. The outstanding features at the necropsy consisted of slight inflammatory changes in the pancreas with normal islands and a definite severe encephalitis in the cerebellar vermis involving chiefly the pyramid and uvula. The nucleus periventricularis and the globus pallidus were normal. The question naturally arose, therefore, whether a lesion in the cerebellum could cause glycosuria. This was not a

new theory because it had occurred to Claude Bernard in his puncture of the medulla. Bernard originally punctured the cerebellum as well as the medulla and he raised the question whether injury of the cerebellum did not have a part in producing the glycosuria. In 1923, Dresel and Lewy mentioned the possibility of causing glycosuria by injury of the cerebellar vermis. Papilian and Cruceann (1925) found hyperglycemia in dogs after injury of the vermis. Shinosaki inflicted injuries on the cerebellar vermis in different areas in twenty dogs and noted the blood sugar content, the chlorides and the body temperature. He divided his results into four classes: very strongly positive, strongly positive, weakly positive and negative. 1. Very Strongly Positive Group: To this group belong cases in which the blood sugar content was 0.19 per cent one hour after operation and in which the hyperglycemia lasted longer than one day. Three dogs fell into this group. The hyperglycemia lasted from one to four days and in one instance rose as high as 0.20 per cent. In all three of the dogs, the uvula was destroyed, especially the cortex. The medulla was uninjured. 2. Strongly Positive Group: To this group belong cases in which the blood sugar was 0.17 per cent one hour after operation and in which the hyperglycemia lasted over three hours. Four dogs came into this group. The lesions were chiefly in the uvula and were superficial; that is, they did not go deep in the uvula. In two of the cases, the pyramid and nodule were included in addition to the uvula. 3. Weakly Positive Group: To this group belong the cases in which the blood sugar was 0.15 per cent one hour after operation and in which the hyperglycemia lasted longer than one hour. Six dogs were included in this group. The lesions were largely in the posterior part of the pyramid. The uvula was intact. 4. Negative Group: To this group belong those cases in which the sugar content was under 0.13 per cent one hour after operation, and in which the hyperglycemia lasted less than one hour. This group included seven dogs. In all of them the vermis was entirely intact, while the lesion was found to be within the hemispheres.

Summarizing his results in another way, Shinosaki concludes that: (1) hyperglycemia due to destruction of the cerebellar hemisphere does not last longer than one half hour; (2) hyperglycemia due to a superficial lesion of the pyramid lasts only about ten minutes after the operation, while severe injury of the pyramid causes a hyperglycemia of one hour or more; (3) destruction of the superior vermis in front of the fissura secunda causes no hyperglycemia, while behind it there is a severe hyperglycemia.

Shinosaki ran only one control experiment to determine whether the hyperglycemia was the result of narcosis and obtained a negative result. He concluded that lesions behind the fissura secunda—i. e., in the uvula—produce a marked hyperglycemia lasting as long as four days. Changes in body temperature or chloride content do not occur.

ALPERS, Philadelphia.

BLOOD GROUPING IN THE INSANE. ALEXANDER PILCZ, Jahrb. f. Psychiat. u. Neurol. **45**:120, 1927.

Considering the fact that belonging to a certain blood group is a constitutional factor, Pilcz finds that psychopathic persons, the genuinely periodically insane and persons predisposed to pathologic confusional states, and partly also persons with epilepsy (group III) bear a certain relationship to persons with general paralysis and schizophrenia, both of which are closely related to each other from the point of view of blood grouping. These observations are in full accord with the principles of heredity as manifested in clinical psychiatry. Conditions are entirely different in arteriosclerotic and senile psychoses as well as in hysteria and in conditions variously designated as "psychogenic depressive states," "affects" and in persons who attempt suicide.

Comparing the figures of the rarer and therefore most interesting groups I and III in arteriosclerotic and in senile persons, there are 11.1 per cent in group I and 20.4 per cent in group III—figures that are decidedly lower than in psycho-

pathic persons and the periodically insane, although they approach more the figures of both of these forms than the corresponding figures for general paralysis and dementia praecox. It is well known that it is in cases of arteriosclerotic and senile psychoses that the heredodegenerative psychotic predisposition does not play any particular rôle. Aschaffenberg and others long ago called attention to the greater frequency of apoplexy in the ascendants of melancholic persons, and the author's investigation of 2,000 insane persons, from a hereditary point of view, has also shown that, excluding arteriosclerotic and senile dementia and general paralysis, apoplexy was a more common occurrence in the ascendants of melancholy persons. In this connection Pilcz emphasizes the relationship between cerebral arteriosclerosis (calcification) and manic-depressive insanity, for occasionally the first attack of a periodic psychotic episode will manifest itself in association with an attack of apoplexy. Bearing in mind the heredodegenerative predisposition and disposition to general paralysis, clinically as well as from the point of view of blood grouping, one can hardly deny that there must be some relationship between cerebral arteriosclerosis and manic-depressive insanity; the manic and especially the depressive states observed in cerebral arteriosclerosis and senile dementia as well as the melancholia of aged persons and the periodic psychic disturbances in cases of "cerebral scars," etc., bear ample evidences to this relationship. In view of all these facts, the circumstance that persons with arteriosclerotic and senile psychoses show a blood grouping which is relatively intermediate between that of manic-depressive insanity and general paralysis, might be of some significance. The relationship, as far as blood grouping is concerned, between the heredodegenerative diseases and the hysterical psychoses on the one hand, and between the psychogenic depressions on the other, does not permit any definite conclusions. The figures for groups I and III differ essentially from those in psychopathic persons and the periodically insane, and while they approach more those of general paralysis they differ considerably from each other.

It can readily been seen that some of the results of blood grouping studies among the insane are in harmony with many of the well known psychiatric principles of heredity, while others cannot be reconciled. This, however, is not surprising when one bears in mind that nature refuses to adhere to scientific classifications and that concepts of disposition and immunity can be evaluated only quantitatively, and furthermore, that although belonging to a particular blood group is undoubtedly a constitutional factor, it represents only one of many, and as yet unknown constitutional factors which are of greatest significance for the predisposition of certain persons to certain morbid states.

In full realization that the last word on this subject has not as yet been said, the author believes that his investigation justifies the following statement as a working hypothesis: Among the constitutional factors which play a rôle in the disposition to heredodegenerative psychotic conditions may also be included the factor of belonging to blood groups I and especially III; such is not the case with persons who are predisposed to general paralysis and dementia praecox. Belonging to blood groups I and III is also a constitutional factor, though to a lesser extent from a quantitative point of view, in persons predisposed to arteriosclerotic and senile psychoses, but does not play any rôle in hysterical persons and in those with tendencies to psychogenic depressive states.

In conclusion, Pilcz presents the following observation: Psychopathic persons, and those with an epileptoid alcoholic reaction constitute the greatest contingent of group III. According to Gundel, hardened and habitual criminals also show unusually high figures in group III. Furthermore, blood grouping studies in various races have shown that the percentage frequency of group III rises as one goes from northwestern to southeastern countries, reaching its maximum in gypsies and negroes. "These facts" says the author "remind one of Lombroso's much contested conception that 'uomo delinquente nato' represents a regression to a primitive type."

KESCHNER, New York

CHANGES IN THE BRAIN IN SEVERE DIABETES MELLITUS. CHIKAZO INABA, Arb. a. d. neurol. Inst. a. d. Wien. Univ. **29**:315 (Sept.) 1927.

Inaba examined the brains from four cases of severe diabetes mellitus. Especial attention was paid to those structures which are said to play an important part in carbohydrate metabolism. The region of the dorsal nucleus of the vagus in the medulla was carefully examined, while in the midbrain the hypothalamic region, tuber cinereum, nucleus mammillo-infundibularis, nucleus supra-opticus, nucleus paraventricularis and the nucleus reticularis hypothalamicus of Malone were investigated. F. H. Lewy, who has established the central innervation of those glands having to do with carbohydrate metabolism, concludes that this process is regulated by cells in the medulla oblongata lying in the region of the dorsal vagus nucleus. These cells are in turn governed by cells of the nucleus periventricularis which lies in the hypothalamic region, and, finally, by another center in the globus pallidus. The nucleus periventricularis is in reality composed of several groups. Most caudad is the nucleus mammillo-infundibularis which begins in the region of the corpus mammillare and extends orally in the regio hypothalamica to about the middle of the thalamus. It lies immediately adjacent to the ventricle, and just ventral to it, in the tuber cinereum itself, lies the ganglion of the tuber cinereum. Orally from this region lie the nucleus paraventricularis hypothalamicus and nucleus supra-opticus.

According to Dresel, after the occurrence of a lesion in the region of the dorsal vagus nucleus, there is a retrograde degeneration in the midbrain involving the nucleus periventricularis. Dresel also assumes that the fields H 1 and H 2 of Forel represent a connection between the striatum and these cell groups. The latter assumption, however, is still in the controversial stage. Spiegel believes that the tuber cinereum is concerned with the heat regulation of the body, and also that it has something to do with renal activity. This has not yet been proved. Camus, Gournay and Legrand experimentally produced lesions of the tuber cinereum in rabbits by the introduction of foreign bodies. In all cases in which a glycosuria appeared, the hypophysis as well as the tuber cinereum was destroyed. These same authors also found changes in the nucleus paraventricularis. They differentiate between polyuria and glycosuria, believing that lesions of the nucleus of the tuber cinereum are responsible for the former, and lesions of the nucleus paraventricularis for the latter. Numerous other authors have noted changes in the tubero-infundibular region, particularly of the nucleus periventricularis, in cases of severe diabetes. Some others observed changes also in the region of the dorsal vagus nucleus.

The changes in Inaba's four cases were almost identical in all. In none of them were there any changes in the region of the dorsal vagus nucleus. In the midbrain only the cells were examined because the fibers of the tuber are so delicate that they stain imperfectly. In the nucleus paraventricularis all of the cells were absolutely intact. The same was true for the ganglion of the tuber cinereum. On the other hand, the nucleus supra-opticus showed some cellular changes in the caudal portion, and there was severe degeneration of the cells of the nucleus mammillo-infundibularis. These degenerations correspond in all respects to those described by F. H. Lewy and his co-workers, and have certain characteristics peculiar to themselves which differentiate them from agonal changes. In all four cases the globus pallidus remained intact.

The question now arises whether or not these changes have any connection with diabetes mellitus. One must not forget that fibers in this region run to the hypophysis and some of them arise in the nucleus supra-opticus. Since changes were found in the caudal portion of the nucleus supra-opticus, one must consider whether or not the innervation of the hypophysis was in some way interfered with. Inaba believes, however, that changes in the nucleus mentioned are slight and that probably only a small part of the fibers to the hypophysis arise in this region. One must conclude, therefore, that since the

nucleus mammillo-infundibularis plays an unimportant part in the innervation of the hypophysis, and since the main lesion involves this structure, the interference with the nerve supply of the hypophysis is slight.

Whether or not the lesion of the nucleus mammillo-infundibularis has a determining significance in diabetes mellitus cannot be decided from these observations. One can only say that in cases of severe diabetes mellitus these structures appear to be damaged and seem to bear some relation to the glands regulating carbohydrate metabolism.

KAMMAN, Saint Paul.

VEGETATIVE CENTERS IN THE CENTRAL NERVOUS SYSTEM. S. A. SARKISSOW, J. f. Psychol. u. Neurol. **35**:28, 1927.

A boy, aged 14, was admitted to Rossolimo's clinic in Moscow in December, 1924, with the history that since March, 1924, he had been having attacks of vertigo and epileptiform seizures preceded by vomiting. The essential symptoms were (1) amnesic aphasia, (2) extrapyramidal motor disturbances: almost continuous choreiform twitching of the limbs on the right side; attacks of petit and grand mal with loss of consciousness and tonic convulsions, more marked on the right side of the body; no biting of the tongue and no urinary incontinence. (3) vegetative nervous system symptoms: (*a*) excessive fatty pads in the anterior wall of the abdomen, near the breasts, around the hips and in the gluteal region (feminine type) with retarded development of the gonads and secondary sex characters; (*b*) increase in temperature which lasted five months and was indefinite in character; the highest temperatures reached were simultaneous with the convulsive seizures; (*c*) glycosuria on the days during which the fever and convulsions occurred; the ingestion of glucose was followed by convulsions, hyperglycemia and glycosuria; (*d*) moderate night sweats, more marked on the right side of the body with a similar reaction following pilocarpine injections; (*e*) excess of amorphous deposits in the urine. There were also mild pyramidal tract signs on the right side of the body. The fundi and pupils were normal and the Wassermann reactions of the blood and of the cerebrospinal fluid were negative. The diagnosis rested between encephalitis and cerebral neoplasm in the left hemisphere—in the subcortical ganglia. Encephalography confirmed the diagnosis of tumor and its localization. Operation was not performed and at the end of February, 1925, the boy developed "status epilepticus" during which he died.

Necropsy revealed: general hyperemia of all internal organs, excessive subcutaneous fat in the abdomen and gluteal region, and very small testes. Microscopic examination of these organs gave negative results. The meninges were swollen and hyperemic. No tumor was found and there was no dilatation of the ventricles nor of the aqueduct of Sylvius. Microscopic examination showed marked hyperemia and dilatation of the blood vessels in the meninges. The vessel walls showed round cell infiltration. The cortex also revealed cell changes, especially in the region of the left central convolution, consisting of alterations in form, disintegration and neuronophagia. The subcortical ganglia showed an increased number of vessels, the walls of which were also infiltrated with round cells and in some areas lacerated; minute hemorrhages and thrombi were also present. These vascular changes were especially marked in the subthalamic region of the left hemisphere. In this area the perivascular spaces were dilated and there were numerous foci of edema and softening surrounding the vessels. The lenticular nucleus, claustrum and globus pallidus appeared unusually pale with the Heidenhain stain. This pale area also included the island of Reil. There was also an increase in the glia with broken down myelin fibers, vacuolated cells and evidences of neuronophagia. No such changes were observed in the corresponding regions in the right hemisphere. Striking cellular and fiber changes were also observed in the left corpus striatum and pallidum. The left pyramidal tract showed marked discoloration, especially in the postero-internal portion of the pons; the degeneration of this tract could be traced into the cord. The cerebellum was normal. The hypophysis did not show any changes. The

cells of the sympathetic cervical ganglia showed slight alterations. The entire process was one of subacute inflammation of unknown origin which involved mesenchymatous and parenchymatous structures, especially in the subcortical and thalamic regions on the left side.

The clinical history and anatomopathologic conditions fully confirm the views held by most observers as to the vegetative-regulating rôle played by the subthalamic region. The case also illustrates that dystrophia adiposogenitalis may exist without changes in the hypophysis, and that in some instances this syndrome may be due to changes in the hypothalamus. The changes found in the posterior speech zone also account for the amnesic aphasia. Finally, the case is an object lesson in showing the care that one must take in the interpretation of roentgen-ray observations following encephalography; the latter showed diminution in the size and change in contour of the left ventricle which led to the diagnosis of cerebral neoplasm which could not be substantiated at necropsy.

KESCHNER, New York.

ANTEROLATERAL TRACT SECTION. O. FOERSTER, Arch. f. Psychiat. **81**:707 (Sept.) 1927.

Foerster reports his experiences with anterolateral tract section which he has performed in eight cases. He first discusses the question of how many segments are involved in the crossing of the pain and temperature fibers. His experiences show that this crossing is completed in one segment, and a complete section of the anterolateral tract at the upper part of a given segment may leave unaffected only those skin areas which correspond to this segment, all the lower ones showing analgesia and athermesthesia. Inside the anterolateral tract itself there is a certain segmental distribution of the fibers with the fibers belonging to the lowest segments lying in the extreme anterior and lateral parts, whereas the fibers coming from the upper segments lie further posteriorly and internally, so that a chordotomy that does not reach far enough internally may miss some of the segments nearest the site of operation. It is thus that the idea originated that the crossing of the fibers occurs in more than one segment. The lowest sacral zones, however (penis, scrotum, labia majora and minora, perineum, anus and urethra), may not be affected by the chordotomy whether unilateral or bilateral. As a rule, a complete anterolateral tract section causes disappearance of all pain sensations of the skin. The deep pain and visceral pain sensibilities, however, may return after a while, although they too disappear at first. This would suggest that these pain fibers have other routes. It is possible that the columns of the posterior horn are responsible for this, or that the posterior tracts can conduct pain impulses. These must be regarded as auxiliary tracts for pain impulses taking up this function after the anterolateral tracts have been sectioned. As a rule, they serve this purpose only for stimuli of a visceral and deep sensibility type. Occasionally, however, the skin sensation may be conducted in this way also.

Outside of pain, the temperature sensation is affected by this operation. The athermesthesia following it is complete for the whole body, as there are no specific visceral or deep temperature sensations. Tactile sensations are supposed to be conducted along two routes: (1) the homolateral posterior tract, and (2) the opposite anterolateral tract. The author has not found the least change in the tactile sensibility following an anterolateral tract section. This would seem to be due to the fact that the posterior tracts completely replace the ones sectioned. The pressure sensations behave in the same way as the tactile, with little if any change following the section. The vibratory sense too, is not affected by anterolateral section, but is practically absent following posterior tract section. This preservation of vibratory sense following anterolateral section does not mean that this sensation is left altogether as before the operation. The concomitant psychic component seems to be lost, i. e., a feeling which is somewhat similar to that of tickling or itching. Along

with pain and temperature sensations, then, these indefinite psychic concomitants of the vibratory sense are lost too. Sense of position and kinesthetic sense are not affected.

The operation is indicated practically in cases of pain caused by root processes. The author has carried out chordotomy in cases of gastric crises in tabes; this was successful in some cases but not in others. Superficial pain sensations, however, practically always disappear following the chordotomy. The author has also attempted this procedure in cases of rigor and tremor of the pallidal type. The results, however, are not sufficiently definite to admit of conclusions. In performing the operation, the surgeon should determine the site by the height of the pain zones, always taking the upper part of the segment immediately above the zone. A comparatively wide laminectomy is necessary. Superficially, the border between the anterolateral and posterolateral tracts is marked by the dentate ligament. The chordotomy should be perperformed anterior to this ligament. Bleeding is slight.

MALAMUD, Foxborough, Mass.

THE RELATION BETWEEN VERTEBRAE AND SPINAL CORD AND THE OCCURRENCE OF TRANSVERSE PARALYSIS IN CHONDRODYSTROPHIC DWARFS. JULIUS DONATH and ALFRED VOGE, Ztschr. f. d. ges. Neurol. u. Psychiat. **111**:333 (Nov.) 1927.

In an earlier contribution, Donath and Voge pointed out a fact that, they state, had not hitherto been noted: the dorsolumbar region of the spinal column shows a constant marked deviation from its normal lordosis, and only in this region (from the twelfth dorsal to the third lumbar) do the vertebrae show the more or less pronounced wedge-shaped deformity. In the present contribution they take up the question of the narrowing of the vertebral canal and the occurrence of disorders of the spinal cord in chondrodystrophic dwarfs. Since the contribution of Breus and Kolisko it has been known that there is a definite narrowing of the spinal canal in chondrodystrophic dwarfs. They concluded that the narrowing was chiefly in the anteroposterior diameter (frontal stenosis) but that it occurred also in a sagittal direction. They attributed the condition to a synostosis of the bones of the vertebrae. Since their contribution it has been the custom to speak of the frontal stenosis of the vertebral canal, although in several instances so reported there has been actual narrowing in the sagittal diameter, often more pronounced than anteroposteriorly. From two observations of their own, Donath and Voge state that it is a misnomer to speak of frontal (anteroposterior) stenosis of the vertebral canal because the narrowing may be most marked in the sagittal or anteroposterior diameters, or equally present in both.

It is certain that changes in the vertebrae in chondrodystrophic dwarfs can cause injuries to the spinal cord. Lampe described them in a dwarf who died soon after birth. Here there was marked narrowing of the canal with compression of the cord in the cervical region at the level of the epistropheus. Collmann reported a markedly narrowed foramen magnum in an eight months' fetus of the chondrodystrophic type. Other cases have been reported in adults. Falta reported a case of spastic paraparesis in chondrodystrophy which he attributed to pressure on the cord by narrowing of the vertebral canal. Kemenyffi reported a case with reflex disturbances in the lower extremities which he explains similarly to Falta. Maas reported a similar case.

Donath and Voge report a case with compression of the cord; necropsy showed a transverse lesion in the upper lumbar cord causing an ascending degeneration in the region of the medial part of the dorsal columns, and a descending degeneration in the pyramidal tracts. This is not the picture of a complete transverse lesion; they considered the localization of the lesion in the medial part of the dorsal columns of special interest. This area is supplied by the arteria septi posterioris and the lesion is related probably to interference

with the blood supply of this artery. The picture was one of incomplete transverse myelitis. The immediate cause of compression is found in exostoses resulting from localized spondylo-arthritis deformans. ALPERS, Philadelphia.

THE SO-CALLED SMALL ROUND CELL INFILTRATIONS: I. POLIO-ENCEPHALITIS AND ACUTE EPIDEMIC ENCEPHALITIS. N. A. MICHELS and J. H. GLOBUS, Arch. Path. **4**:692 (Nov.) 1927.

The origin of the various types of cells that appear in perivascular infiltrations has been a subject of discussion for many years. The conflicting opinions may be summarized as follows: (1) the cells have an exclusively hematogenous origin; (2) they arise from preexisting connective tissue cells; (3) they have a mixed origin (Maximow); (4) they arise preponderantly from the vascular endothelium (Foot). In current contributions the discussion centers about the position taken by Maximow and Foot.

The authors consider that inflammatory lesions in the central nervous system offer particularly favorable opportunity for the study of the source of origin of the cells in the perivascular infiltrations because of the strong tendency of the inflammatory elements to be restricted to the so-called adventitial spaces for long periods while they undergo various morphologic changes. They studied seven cases of polio-encephalomyelitis and five cases of acute epidemic encephalitis. These histologic studies seem to show that the vast majority of the infiltrative elements in the adventitial spaces, as well as those in extravascular territory, have filtered out in some selective fashion through the walls of the blood vessels. This view is supported by the stream like orientation and migration of the lymphoid cells in the vicinity of the blood vessels and by the uniform presence of emigrating lymphocytes and large mononuclear cells. The fact that, in some instances, emigration pictures are extremely numerous, while in others relatively few cells were seen in transit, suggests that the cells are extravasated in showers. After extravasation, the behavior of the lymphoid cells varies. Some remain as lymphocytes and large mononuclear cells, others undergo differentiation and become transformed into polyblasts, macrophages, granular cells and occasionally plasma cells.

In not a single instance did the endothelium of the blood vessels exhibit cytogenic activity nor were cells observed originating from the so-called adventitial cells or from other fixed perivascular connective tissue cells. Granulocytes, eosinophils or mast leukocytes did not play any rôle in the inflammatory process. Extravasation of red blood cells was noted in each case and, while generally restricted to the perivascular zone, often assumed hemorrhagic proportions. In cases of encephalitis that have run a stormy course with a sudden termination the predominant histologic picture is that of numerous hemorrhages with an unusual sparsity of typical small round cell infiltrations. A tentative explanation of this phenomenon may be the fact that the toxic agent reaching the blood vessel is overwhelming in its potency, and injures the wall to such an extent that only a partial selective filtration of blood element occurs, but a massive amount of blood contents escape to the general parenchyma.

PEARSON, Philadelphia.

THE HEREDITARY BEARINGS OF SENILE DEMENTIA. HANS LUDWIG WEINBERGER, Ztschr. f. d. ges. Neurol. u. Psychiat. **106**:666 (Dec.) 1926.

The idea that those who have succumbed to an attack of senile dementia have never been normal mentally is not a new one. Berye (1910) asserted that the dementia of old age could be definitely related to a predisposition to dementia praecox. Meggendorfer (1924) made an extensive study of the problem and found that in cases of senile dementia one is really dealing with latent schizophrenia which first becomes manifest through atrophy of the brain. Meggendorfer found in his series seventeen cases of dementia praecox and fifty-eight

of schizoid psychopathy; among 540 family relatives, he found forty with schizoid conditions; 138 with psychopathic and other neuropathic conditions, and 362 healthy persons; among 234 children of senile dements, he found five with schizophrenic and twenty-five with schizoid conditions; he found a greater tendency to inheritance of disorders of the nervous system in families of persons with senile dementia as well as in those of cerebral arteriosclerotic patients.

The cases reported in this article were not followed through necropsy. The average age of the patients studied was 75.8 years. In twenty-five clinic cases, Weinberger found five patients with schizoid personalities. Four of these showed signs during the illness which were more or less characteristic of schizophrenia. In three cases of psychopathic personality, there was a definite history of excessive use of alcohol; in twenty-five other cases, four patients showed schizoid personalities before the onset of the psychoses, five were alcoholic and one was addicted to the use of morphine. The clinical picture in all the cases showed certain similarities to dementia praecox, in the cases of those without schizoid personalities as well as those with a schizoid make-up. Psychopathic personalities were disclosed in eighteen of the fifty-one cases, fewer than in Meggendorfer's series. The number of alcoholic patients is striking.

Weinberger found among the relatives, parents and children of his fifty-one patients with senile dementia only a few cases of dementia praecox, and considered it improbable that there is a connection between dementia praecox and senile dementia. The number of schizoid conditions in his series were too few to bear out the contention that dementia praecox and senile dementia are related. He sees no reason to believe that the occurrence of senile dementia in a person augurs poorly for his descendants or indicates mental weakness in his forbears.

ALPERS, Philadelphia.

THE SO-CALLED PARADOXIC LIGHT REACTIONS. LOWENSTEIN, Monatschr. f. Psychiat. u. Neurol. **60**:48 (Oct.) 1927.

For over a year the author had under observation a case of general paralysis in which repeated examinations, taking care to exclude sources of error, showed light reactions at times normal in direction, and at other times paradoxic. The paradoxic reactions varied: the "Bechterew and Westphal type" — pupillary dilatation preceded by a minimal contraction; the Kehrer type — dilatation after a prolonged latent period; and the true paradoxic reaction, showing either slow and inadequate, or prompt and adequate primary dilatation of the pupil on light stimulation, all appeared at different times.

In a case of tabes dorsalis, repeated stimulation with a weak light produced a slight primary dilatation after the second stimulus, and a marked dilatation after the third.

Paradoxic light reactions can be produced in any normal person by means of exhausting the light reflex by rapidly repeated light stimuli of medium intensity. If one stimulates repeatedly in this way, one finds the light response becoming slow and inadequate and the latent time increasing, and after from 12 to 15 stimuli, or even fewer, the paradoxic reaction develops.

The true and false paradoxic reactions, previously reported in pathologic conditions, must be judged according to analogy with these physiologic exhaustion reactions. The previous division of these cases into groups, depending on whether there was: (1) a prompt primary dilatation, (2) a primary dilatation with a long latent period, (3) a dilatation preceded by a narrowing and (4) on shading the pupil a contraction with or without a primary dilatation, is not justified. All these types are expressions of some unknown pathologic process affecting the intercalary neuron system, the symptomatic expression of which finds absolute analogies in physiologic exhaustion. Contrary to Behr, however, one should not assume that in these pathologic cases the light stimulus itself produces the exhaustion. One must assume that the exhaustion is already present, as an expression of a lesion affecting the sphincter nucleus.

The consensual light response, which in normal persons is analogous to the direct response, in these pathologic cases shows differences. The direct light reactions may be slow but normal in direction, whereas the consensual response may be paradoxic.

Response to sensory stimuli was generally slow, but normal. But true paradoxic sensory reactions were found; i. e., narrowing of the pupils following stimuli. No explanation is yet possible.

SELLING, Portland, Ore.

ARCHICAPILLARIES AND MENTAL DEFICIENCY. H. DELBRUECK, Arch. f. Psychiat. **81**:606 (Sept.) 1927.

The author reports the results of an investigation of the structure of the capillaries in children of different types (both mentally deficient and normal) along the lines suggested by W. Jaensch. The latter, following the work of O. Müller, claims that in a great majority of feebleminded children the end capillaries show a distinct deviation from the normal in the form of faulty development. Hoepfner gives a classification of these types of capillaries: The archicapillaries which tend to assume the shape of a horizontal network; these should disappear at the end of the first year, giving rise to the thin vertical capillaries of the normal child by going through a series of changes which are called intermediary types. Pathologically, either one of these primitive forms may be found at an age when they should have disappeared (giving place to the normal type) or the transformation may proceed along abnormal directions, developing all types of bizarre pictures. The studies are made by photomicrography of the capillaries of the fingers. The author has found most of the types described by Hoepfner, but he could not substantiate the relation of such occurrences to mental deficiency. He distinguishes five of the types described by Hoepfner: productive faulty development, intermediary, intermediary deviations, neurosis type and neocapillaries. Four hundred and fifty children were examined, some of them being school children of normal and superior intelligence, others of special classes for mentally deficient children.

The results could be summed up as follows: there were practically as many pathologic forms among the normal and superior children as among those belonging to special classes. Those that showed archicapillaries, both of the normal as well as of the mentally deficient children, did not show any difference in their intellectual faculties from those whose capillaries were of normal shape. An investigation of the relation between special neurotic manifestations and these pathologic capillaries shows no correlation between the two. Some investigators suggest that pathologic capillary forms of this type are met with in children who show other stigmas of degeneracy. The author found no such correlation.

In his conclusions the author is of the opinion that although a pathologic maldevelopment of the capillaries, as suggested by Jaensch, does exist, the relation that they bear to mental deficiency, as suggested by this author, could not be substantiated.

MALAMUD, Foxborough, Mass.

PFROPFSCHIZOPHRENIE. R. NEUSTADT, Arch. f. Psychiat. **82**:78 (Oct.) 1927.

Under the term Pfropfschizophrenie, one usually understands a psychosis which in its essential features and course corresponds to the criteria of a schizophrenic process, and which occurs in a person originally a mental defective. The statistics of the frequency of its occurrence differ with different authors; for instance, there is a great divergence of opinion concerning the occurrence of the psychosis in the textbooks of Kraepelin and Bleuler. The reason for these divergencies is to be looked for primarily in the rather indefinite limitations of the concepts of feeblemindedness and schizophrenia. The author is of the opinion that the term feeblemindedness should be restricted to intelligence defects, either congenital or acquired in infancy, which remain

stationary. Even with this restriction, the concept does not include uniform material. It would include constitutionally familial types, endocrine disturbances and pure cerebral defects. The common features to be stressed would remain the early manifestation, predominance of intelligence defects and the absence of progression. It is especially important to exclude such defects that might have been caused by an early schizophrenic episode which should be looked on as part of the psychosis.

Similarly, the application of the term schizophrenia should be somewhat restricted, for one finds psychoses that develop on the basis of feeblemindedness which superficially resemble a schizophrenic process in that they show some of the symptoms, and yet the underlying mechanism is not at all that of a schizophrenia. Two cases are reported, in both of which the history showed a definite intelligence defect, either constitutional or acquired early in life. In later life (in the first case at the age of 40, in the second case at the age of 35), acute psychotic episodes developed with paranoid delusions of persecution, hallucinations and periods of excitement. In both cases a diagnosis of Pfropfschizophrenie was made. Both patients recovered after a comparatively short time, and returned to the previous state of moderately marked intelligence defect. The diagnosis suggested by the author is that of an episodic psychosis with mental defect. Just what the relations of these episodic outbreaks to different psychoses are is not clearly understood. Some of them may be of the manic-depressive type; others may have some psychogenic background; still others may be epileptiform in nature. So far as the author can see, however, they bear nothing but a superficial resemblance to a schizophrenia, and the conclusion that the author comes to is that only a small part of the so-called Pfropfschizophrenie really belongs with schizophrenia.

MALAMUD, Foxborough, Mass.

THE QUESTION OF DIFFUSE SCLEROSIS. OSKAR GAZEL, Ztschr. f. d. ges. Neurol. u. Psychiat. **109**:418 (July) 1927.

Gazel reports a case in a boy, aged 8, who following an attack of measles developed a decline in mental capacities and a spastic-paretic gait. The condition grew steadily worse; his intelligence decreased so that he could no longer read, write or cipher, and he developed marked spasticity in all four extremities. After about a year he lost the power of speech. He developed athetosis-like movements in the upper extremities, followed by disturbances in swallowing, and after an illness lasting one and one-quarter years died of pneumonia. Necropsy revealed many areas of sclerosis of the brain. The internal capsule, and the direct and indirect pyramidal tracts were intensely degenerated. Foci of sclerosis were found in the optic nerve, gyrus cinguli, anterior commissure (which was markedly affected), temporal lobes, optic tract, pons, middle cerebellar peduncle, cerebellar hemispheres, and nucleus dentatus. They showed a predilection for certain systems; the neocerebellum was involved in preference to the paleocerebellum. Certain fiber systems also, such as the arcuate fibers and the trigeminal fibers, showed a marked resistance to the disease process. Gazel looks on the degeneration in the capsule and in the pyramidal tracts as a secondary manifestation. The nature of the process in the white matter of the cerebrum may be: (1) primary injury of the myelin sheaths; (2) primary inflammation; (3) primary glial proliferation.

Gazel separates the case he reports from the group of encephalitis perixialis diffusa of Schilder which contains many cases not belonging there. He believes his case is a new syndrome similar to cases described by Scholz, Flatau, Siemerling, and Creutzfeldt and Haberfeld. The cases described by these authors all show the combination of a progressive spastic paralysis of all extremities with a progressive decrease in intelligence. The disease begins in childhood and is characterized by its progressive nature. Decrease in vision

is a frequent concomitant. Anatomically, a large part of the white matter of the cerebrum and cerebellum is destroyed by symmetrical foci. The pyramidal tracts are severely injured. The disease is difficult to differentiate from multiple sclerosis.

ALPERS, Philadelphia.

THE TREATMENT OF HEADACHE. ARTUR SCHÜLLER, Wien. klin. Wchnschr. **40**:1331, 1927.

In this brief article, Schüller takes up the treatment of patients with headaches. He purposely avoids what he terms gross organic headaches, such as the headaches from tumor of the brain or syphilis. He is more interested in the headaches which are usually termed nervous, migraine, toxic and the like. It is his impression that patients with so-called nervous or neurasthenic headaches should be treated by rest. Closely allied to this group are the so-called fatigue headaches, especially those associated with eye strain and mental exhaustion.

He believes that there is a large group of so-called rheumatic head pains which occur especially in people who have to work in damp, cold or drafty places. The patient with this type of headache is best treated by warm applications, either dry or moist. Massage and electricity are frequently beneficial in this group. It is his opinion that persons with the so-called traumatic headaches are best treated along similar lines. Taking up the group of headaches associated with circulatory disturbances, he naturally advises treatment of the underlying condition, whether it is anemia, hypertension, nephritis or arteriosclerosis. The use of calcium diuretin and nitrites is especially advisable, although this group of patients will also show improvement under treatment with preparations containing bromides. It is rather interesting that, in his migraine group, he has no new or specific therapy. He says that he has seen considerable improvement in patients who have been taking small repeated doses of phenobarbital. He merely mentions the so-called peptone cure. In the treatment of patients with neuralgia, under which the author discusses especially trigeminal and occipital neuralgia, he emphasizes the need for the eradication of all possible foci, and from his discussion one would gather that the teeth and sinuses are frequently at fault. It is rather strange that he does not mention injection of alcohol or section of the posterior root.

The author constantly warns that one must not assume that a headache is of a functional origin but must constantly bear in mind the possibility of a tumor of the brain, syphilis or metastatic lesions.

MOERSCH, Rochester, Minn.

THE INTRAVENTRICULAR TREATMENT OF PARESIS. CESTAN RISER and PÉRÈS, J. Nerv. & Ment. Dis. **66**:227 (Sept.) 1927.

Intravenous injections of arsphenamine having proved incapable of improving patients with general paralysis to any degree, the authors reviewed the literature on the intraventricular method of treatment, including the work of Hammond, Sharpe, Campbell, Sands, Knapp and others. These observers have believed that the intraventricular method is more satisfactory in reaching the nerve cells of the cerebrum. By the intraventricular injection of iron ammonium citrate and potassium ferrocyanide in an epileptic patient who died six hours later, the authors found the walls of the lateral ventricles impregnated with the precipitated iron, but only to a depth of from 1 to 2 mm. The walls of the small veins showed considerable quantities, but the absorption into the surrounding nerve tissue was superficial, though to a greater depth (from 5 to 10 mm.) than in the ventricles. The authors think that the ventricular fluid does not penetrate the bulk of the cerebral parenchyma and hence cannot be regarded as nutritive to it. Injections in the lumbar region of 15 cc. of iron solution lead to no absorption by the anterior horn cells. A series of eight cases in which injections of arsphenamine were made were recorded. Doses

higher than 30 mg. caused death in the patients studied. In such cases, the arsphenamine had produced a hemorrhagic encephalitis in the cerebrum bounding the ventricles. The authors found the ventricular fluid extremely modified after from one to three injections of moderate doses, but an increased sensitivity to subsequent injections of arsphenamine developed which rendered the method dangerous. An inhibitory action on the secretion of the cerebrospinal fluid by the arsphenamine was observed and was deemed practicable for the treatment in cases of internal hydrocephalus. No recovery from general paralysis was observed in the series of patients studied, and the authors consider that optimism regarding the intraventricular route for treatment is unwarranted.

H. H. Hart, Greenwich, Conn.

Thrombosis of the Arteries of the Spinal Cord. Helge Vedsmand, Acta Psych. et Neurol. **2**:371, 1927.

After commenting on the relative infrequency of thromboses of the spinal cord as compared to the brain, the author discusses the arterial supply of the cord. Then follow the histories in eight cases of thrombosis of the spinal cord. These are as follows:

Case 1.—A man, aged 71, nonsyphilitic, presented symptoms of myelitis; autopsy showed total necrosis of the dorsal cord without signs of inflammation.

Case 2.—A man, aged 28, syphilitic, presented symptoms corresponding to the autopsy findings of necrosis of the upper thoracic region.

Case 3.—A girl, aged 19, syphilitic, developed a paraplegia after treatment with neoarsphenamine; improvement followed.

Case 4.—A man, aged 40, syphilitic, presented diffuse motor and sensory symptoms pointing to minute thromboses in the cervicothoracic transition zone and in the lumbar and upper sacral zones. Improvement occurred.

Case 5.—A man, aged 53, syphilitic, presented disseminated motor and sensory symptoms. He left the hospital.

Case 6.—A man, aged 76, syphilitic, presented signs of conus involvement; the lesion was confirmed.

Case 7.—A man, aged 25, syphilitic, showed signs of general involvement of the anterior spinal artery; improvement followed.

Case 8.—A girl, aged 11, showed signs of probable tuberculous spondylitis involving the upper lumbar region.

In the six syphilitic cases, the Wassermann reaction was negative in the spinal fluid in five, and in the blood in four. In the two cases (2 and 3) treated with arsphenamine only a short interval elapsed between treatment and the appearance of the cord symptoms. In contrast with these are the four not treated with arsphenamine in which the infection had been from nine to fifty-three years earlier. This is in harmony with the views of Nonne and others.

Anderson, Philadelphia.

Subdivisions of the Facial Nucleus. J. W. Papez, J. Comp. Neurol. **43**:159 (April) 1927.

The author calls attention to the explanation generally adopted in recent years for the clinical phenomenon of paralysis of the lower facial with an intact upper facial, to wit, that such a paralysis is really supranuclear and involves the pyramidal or cortical fibers that pass down to the facial nucleus. The assumption is that the entire facial nucleus is supplied from the contralateral pyramid, but that the cells of origin of the temporal branches are supplied by a contingent of homolateral fibers. This point of view is not supported in the present paper.

This generally accepted view gave the investigator the chief interest in the present study in rats, cats, dogs, sheep, guinea-pigs and opossum. Wax models

of the right facial nuclei of the first four mentioned mammals are shown and discussed. Sections of the facial nuclei are shown in which the various cell columns are indicated. A diagram is also included which shows each cell group of the facial nucleus projected on the surface of the neck and gives the connections of each group with facial musculature in the head. This diagram is based chiefly on the results obtained from experiments in a number of rats, cats, dogs, and guinea-pigs in which various branches of the facial nerve were extirpated singly in such a manner as not to interfere with remaining ones. After fourteen days, the medullas were prepared in serial sections and stained by the Nissl method for chromatic changes in the facial nucleus. Removal of a branch of the facial nerve was followed by cell reactions localized more or less definitely in one of the columnar cell groups of the facial nucleus of the same side. This reaction did not affect the nucleus of the opposite side nor any of the other nuclear masses in the medulla and pons. The comparisons of the facial nuclei herein studied lead the author to the conclusion that the facial nucleus of mammals follows a common plan of subdivision associated with the differentiation of the facial musculature and branches of the facial nerve.

STONE, New Haven.

FUNICULAR MYELITIS. M. KROLL, Ztschr. f. d. ges. Neurol. u. Psychiat. **106**:282 (Dec.) 1926.

Kroll points out that the term funicular myelitis designates the outstanding symptom-system or tract changes in the spinal cord. It does not correspond, however, to the pathologic picture, nor does it consider the extension of the process to the brain. It is therefore better to speak of diffuse cerebrospinal degeneration. In a typical case the earliest and most important symptom is the subjective complaint of paresthesia in different parts of the body. Complaints of this nature should merit investigation of the contents of the blood and the stomach. In addition to the cardinal symptoms of the long tracts, there are symptoms of the endogenous tracts in the region of the posterior roots — vague, indefinite sensory disturbances, chiefly of a segmental character, and loss or decrease of the tendon reflexes — often these are the only symptoms of the disease. The spinal fluid is almost always normal. When there are changes of the spinal fluid they are due to syphilis. Exogenous causes can always be found — anemias, bothriocephalus latus, carcinoma, tropical malaria, infections and other conditions. The brain is almost always involved in the disease. In cases without any clinical signs of cerebral involvement there were cell and vascular changes. Many forms of mental disturbances in the form of imbecility and marked disturbances in memory are only preliminary stages of a certain form of cerebrospinal degeneration. The prognosis of the disease is not absolutely bad. There are mild forms and abortive forms which can be cured.

ALPERS, Philadelphia.

A CASE OF OCCLUSION BY EMBOLUS OF THE POSTERIOR INFERIOR CEREBELLAR ARTERY, VERIFIED AT AUTOPSY, WITH PAIN AND HYPERALGESIA TO COLD. KNUD WINTHER, Acta Psych. et Neurol. **2**:399, 1927.

The details of a case of embolism of the posterior inferior cerebellar artery are presented, of which a summary is as follows: A woman, aged 64, suffering from cardiac trouble, fell suddenly with an evanescent loss of consciousness, followed by vomiting and paresthesia of the right hand. Later she complained of numbness, vertigo, headache and difficult deglutition. She manifested a tendency to fall to the left and had cold sensations in the left side of the face. On examination, she was found to have hypesthesia, hypalgesia and thermohypesthesia in the left side of the face, and hypalgesia and thermohypesthesia in the right half of the body. Horner's syndrome, weakness of the left side of the palate, difficult speech, hiccup, hypotonia, and uncertain paralysis of the left extremities completed the clinical picture.

After three months she complained of increasing pain in the left side of the face; the other symptoms persisted. Finally she experienced severe pain in the legs, with paralysis, which was soon followed by death.

An autopsy confirmed the diagnosis of softening in the bulb and cerebellum, in the area supplied by the posterior inferior cerebellar artery. The author considers this case of particular interest for two reasons: (1) less than 100 cases have been reported in the literature since the original description by Wallenberg in 1895; (2) it raises again the question of "central pain" which has been thought to be characteristic of thalamic lesions. He theorizes on the possible simultaneous involvement of the sympathetic fibers with the descending trigeminal root and the spinothalamic fibers. Some support is given for this view.

ANDERSON, Philadelphia.

ENCEPHALOGRAPHY. R. W. WAGGONER, Am. J. M. Sc. **174**:459 (Oct.) 1927.

A thorough review of the literature was made and the various methods of air insufflation were studied. No authentic report of the incidence of mortality in the use of this diagnostic procedure was found. Several methods are discussed and the method used by the author is presented in detail. Maintenance of a uniform pressure in the cerebrospinal fluid system and the very slow, steady injection of air are considered most important. If properly done there are few postoperative symptoms other than moderate headache. The roentgen-ray exposure is made in the upright position with head straight, as tilting prevents even distribution of air. Encephalography may be used in cases of even greatly increased intracranial pressure by first relieving pressure by ventricular tap and then proceeding with the spinal insufflation.

The author is of the opinion that the dangers of encephalography have been somewhat overemphasized in the past and feels that its value in many cases justifies more general use. Advantages over ventriculography are considered to be: (1) ease of performance; (2) better and more complete information of the condition of the intracranial structures; (3) absence of the necessity for the service of a skilled neurosurgeon. Indications for use are given as: (1) cases of supposed traumatic psychosis to determine the presence of injury to the brain; (2) in cases of hydrocephalus for differentiation of type; (3) certain cases of epilepsy; (4) in cases of encephalitis.

A series of ten cases is reported and plates made from some of these cases are reproduced.

KUBITSCHEK, Philadelphia.

PERICARDIAL PAIN: AN EXPERIMENTAL AND CLINICAL STUDY. JOSEPH CAPPS, Arch. Int. Med. **40**:715 (Nov.) 1927.

In view of conflicting results and statements of many writers, the author of this article determined to ascertain, so far as possible, what structures within and adjacent to the pericardium are capable of producing pain. To this end he performed paracentesis in several cases of tuberculous and rheumatic pericarditis. It was found that in those instances in which the pericardium was punctured at the level of the fourth interspace pain was not experienced, while in punctures at the fifth or sixth interspaces pain was felt in the neck. From this it is concluded that afferent fibers of the phrenic nerve supply the central portion of the diaphragm and extend upward from 3 to 5 cm. over the surface of the fibrous pericardium. By careful irritation of the cardiac surface with a fine silver wire introduced through the cannula it was ascertained that pain was not produced.

Coupling these experimental results with a series of clinical observations on various patients with pericarditis, the conclusion seems justified that the presence of pain in pericarditis usually indicates involvement of the tissues outside the pericardium, especially the pleura. Such pleuropericarditis may

cause a variety of pain complexes: involvement near the diaphragm producing referred pain in the neck; anterior mediastinal implication producing direct local pain; dorsal mediastinal inflammation causing dorsal pain.

ANDERSON, Philadelphia.

FUNCTIONAL PSYCHOSES AS EVOLUTION OF PSYCHIC IMPOTENCY. JOHN HOLLAND CASSITY, J. Nerv. & Ment. Dis. **66**:105 (Aug.) 1927.

In the author's opinion, the development of a psychosis in many instances is nothing else than the development of psychic impotency. Hitherto, the subjects of study have been merely patients with neuroses; the author undertakes to study the symptom in the psychoses. He divides his cases into four groups: (1) patients traumatized at weaning, who have been overweaned or improperly weaned, and who either compensated by latent or active homosexuality, or remain sexually, if not intellectually, at a nursing level; (2) patients whose libido is fixed to preadolescent love objects in a fashion latently incestuous; (3) patients sexually traumatized through inadvertent preadolescent sexual indulgence of incestuous nature; (4) those whose love energies are dissipated in avenging imagined parental desertion or neglect. Cassity gives sample histories from each group, illustrating how unfortunate environmental factors seriously interfere with normal psychosexual development, obliging the individual to shift his position and change his psychic attitude toward life in order to reconcile his sexual inadequacies to social or biologic requirements. Assuming a different perspective, he becomes neurotic or psychotic. A sense of waning sex power develops in melancholic patients, in whom the symptoms are a psychologic response to an essentially somatic situation.

HART, Greenwich, Conn.

THREE CASES OF AMYOTROPHY, OF CHARCOT-MARIE. B. H. ARENDRUP, Acta Psych. et Neurol. **2**:14, 1927.

Three unquestionable cases of this type of muscle atrophy are recorded. They occured in one family, in which the disease had appeared for generations and was regarded as an inheritance. The parents had the same affliction, and of the eight children the second, third, fifth, sixth and seventh were affected; there was also a possibility that the fourth child had been affected. The first and eighth child were not definitely affected.

The patient most carefully studied was the fifth child, a man, aged 56, with onset of the disease before the age of 14. There were practically no sensory changes. The distal atrophy was sharply delimited from just above the elbows and knees. There were almost constant tremor; indeterminate reflexes; no ataxia; good power. A sister, the sixth child, aged 54, presented the same symptoms, distinctly less advanced, and with atrophy confined to the hands and feet. The third case was in a nephew, aged 30, and began with a paralytic pes equinovarus some time before adolescence. The electrical reactions were not determined.

ANDERSON, Philadelphia.

"SPECIFIC" SYPHILIS AND PROGRESSIVE PARALYSIS. DR. ERNEST STRAUSSLER, Monatschr. f. Psychiat. u. Neurol. **65**:117 (Oct.) 1927.

It is relatively rare to find miliary gummas in cases of general paralysis. The significance of this is probably that general paralysis is a malignant syphilis, to which the brain does not react adequately. Tertiary syphilis, with gumma formation, represents a more successful defense of the body against the infection, and by the same token spirochetes are seldom found in gummatous lesions. Recent reports of the observation of miliary gummas in cases of general paralysis after malaria treatment suggest that the malaria has served to convert the "nonspecific, diffuse, malignant inflammation" of general paralysis toward the more benign type of a tertiary syphilis. Change of the colloidal gold curve from a

general paralytic to a syphilitic type is also reported under malarial treatment and speaks in the same sense, as does the regression of plasma cells in favor of lymphocytes in a patient treated by tuberculin and malaria as reported by the author.

SELLING, Portland, Ore.

OBSERVATIONS ON CHOREA MINOR. ERICH GUTTMANN, Ztschr. f. d. ges. Neurol. u. Psychiat. **107**:584 (Feb.) 1927.

Although the toxic infectious nature of chorea is well known, a certain number of observers still believe that there is a certain disposition to the development of chorea. In 539 cases of chorea Wallenberg found a history of it in the parents in 2 per cent, and in relatives or offspring in 5 per cent. In 515 cases investigated by Burr, chorea was present in the family in 17.86 per cent. Guttmann was able to collect reports of chorea in families in ten cases that have been recorded in the literature. From these it seems that there is a predisposition to chorea, apart from its occurrence in connection with rheumatic fever. This disposition need not necessarily be a hereditary trait, but can be looked on as a tendency to develop chorea in soil which is prepared for it. Guttmann reports cases of chorea in which catatonia was rather a common precedent in the forbears.

ALPERS, Philadelphia.

UNUSUAL SYMPTOMS OF A BRAIN ECHINOCOCCUS. ALTSCHUL U. DE ANGELES, Monatschr. f. Psychiat. u. Neurol. **66**:325 (Dec.) 1927.

The authors report a case showing general evidence of increased intracranial pressure, a right lateral homonymous hemianopia and two unusual symptoms: a rotatory or negation tic, and peculiar "sleep attacks." The sleep attacks would come suddenly and last several hours; while they persisted the patient would not respond to stimuli and could not be awakened. When the attack was over, he would sit up, rub his eyes and be perfectly clear mentally.

Autopsy showed an echinococcus cyst, the size of a small orange, involving the greater part of the left occipital lobe and extending forward to destroy the subcortical zone beneath the gyrus angularis. The absence of alexia in relation to this localization is discussed.

SELLING, Portland, Ore.

RUMINATION AND PERSONALITY DEVELOPMENT. P. J. TRENTZSCH, J. Nerv. & Ment. Dis. **66**:245 (Sept.) 1927.

The author declares that it is impossible to obtain an accurate insight into any person by cross section study only; he must be studied as a whole and "longitudinally." He records three cases of infants at a few weeks of age who demanded a considerable amount of attention. They were all subject to rumination. They possessed a special personality make-up even at this early age, sufficient to acquire nicknames from their nurses. Rumination should therefore be looked for in the study of neurotic cases.

H. H. HART, Greenwich, Conn.

UNUSUAL POSTENCEPHALITIS SYMPTOM COMPLEX (WITH A CONTRIBUTION TO THE EXPERIMENTAL PRODUCTION OF SO-CALLED SCHAUANFALLE). F. GEORGI, Ztschr. f. d. ges. Neurol. u. Psychiat. **106**:602 (Dec.) 1926.

Among nine postencephalitic patients with ocular attacks whom Georgi has seen in the past two years, two showed new clinical pictures. The patient in one case showed a typical parkinsonism picture with spasm of the eyes; in addition, there was an erythema of one half of the trunk. The other patient did not show signs of parkinsonism, but had well marked ocular attacks. In both cases, hyperventilation, as recommended by Foerster, cleared up the condition.

ALPERS, Philadelphia.

A Quantitative Investigation of the Alleged Independent Operation of Conscious and Subconscious Processes. Ramona Messerschmidt, J. Abnorm. Psychol. **22**:325 (Oct.-Dec.) 1927.

By means of hypnosis and posthypnotic suggestion the amount of work in two different lines, such as addition and reading aloud carried on simultaneously, was measured. These were compared with the amount of work possible when the two things were done separately. The amount of work in the latter experiment was far greater than that where the two activities were concomitant. The results seemed to controvert the idea of strictly concomitant processes.

Hamill, Chicago.

Psychiatry Needs Help. Editorial, J. A. M. A. **88**:407 (Feb. 5) 1927.

Limitations to, as well as opportunities for progress have been discovered in the field of mental hygiene. Truitt insists that what is needed is orientation in the methods of those fields which vitally affect everyone's adjustive personality. He argues by analogy that we treat patients with yellow fever, but we also strive to eradicate the mosquito. Behavior difficulties must be prevented before human misfits are created. Assimilation of the psychiatric point of view by all agencies working for the psychiatric needs of individuals is a crying need.

Chambers, Syracuse, N. Y.

The Treatment of Neurosyphilis. James L. McCartney, Am. J. Syph. **11**:550 (Oct.) 1927.

This twenty page article continues the subject introduced in the July number. Iodine, bismuth, tryparsamide, malaria, serums, psychotherapy and reeducation are discussed just as were arsenic and mercury in the earlier paper. The entire contribution is well summarized in an eight page termination. Since the article is itself an abstract of an entire field, a review cannot be attempted. It does appear to be definite and avoids the vague generalities that are so easy to make.

Anderson, Philadelphia.

The Calcium Mobilizing Hormone of the Parathyroid Glands. Chemistry and Physiology. J. B. Collip, J. A. M. A. **88**:565 (Feb. 19) 1927.

A brief but somewhat detailed account of the chemistry and physiology of the parathyroid and its hormone is followed by Collip's conclusion that the function of the hormone in the normal animal appears to be that of a regulator of calcium metabolism and its action primarily a mobilizer thereof.

Chambers, Syracuse, N. Y.

The Use of Group Rivalry as an Incentive. Elizabeth B. Hurlock, J. Abnorm. Psychol. **22**:278 (Oct.-Dec.) 1927.

The results described in this article seem to advise the use of rivalry among the student population. This is against those modern ideas of education which deprecate grades and competitive examinations. The results described in the article should encourage those working with the feebleminded.

Hamill, Chicago.

Book Reviews

AN INTRODUCTION TO FORENSIC PSYCHIATRY IN THE CRIMINAL COURTS. W. NORWOOD EAST, M.D. Price, $5.00. Pp. 372. New York: William Wood & Company, 1927.

This is a timely and interesting contribution on psychiatry from the standpoint of criminal responsibility. It is not a book on psychiatry. The author is well qualified to write a book of this sort for he has not only lectured on criminology and forensic psychiatry in London University, but also for many years has been chiefly concerned with the ascertainment of mental disorders and defects in accused persons coming before the English courts.

While the procedure in the British courts is somewhat different from the practice in this country, nevertheless the medical aspects are the same, therefore what the author has to say is of equal import to medical jurisprudence in this country. He begins by an excellent chapter on ascertainment in which he gives the various methods of determining the mental condition of the accused. He comes to the conclusion that the mental condition can be arrived at only after consideration of the known circumstances of the crime, the conduct and conversation of the accused relative thereto and a consideration of the motives, temptations or provocations that preceded the act. These must be first established and then fitted together, piece by piece, to form a harmonic whole with the symptoms of the mental disease and defects presented by the prisoner, an eminently sane point of view. The next chapter deals with practice and procedure. It is obvious that the English procedure is a little different from ours. There are many advantages to the Mental Deficiency Act of 1913 which could well be copied by us. The same can be said of the Lunacy Act.

The next chapter deals with criminal responsibility. Mental deficiency or amentia is dealt with in another chapter. The term "amentia" is a good one as is also the term "moral insanity"; this is used much more frequently in England than in the United States. The term should be used more frequently by us.

Then there follow chapters on dementia praecox and the usual types of insanity met with in criminals. The discussions are adequate for the purpose. Lastly there is a chapter on feigned insanity.

Altogether this is an interesting book, and one which contributes greatly to the study of forensic psychiatry.

ESSAYS IN PSYCHOPATHOLOGY. By WILLIAM A. WHITE, M.D., Washington, D. C. New York and Washington: Nervous and Mental Disease Publishing Company, 1925.

Essays in psychopathology is a compilation of eleven papers which covers a number of subtopics. Two papers are book reviews; one is a review of a recent accomplishment; the remainder are appreciations of new methods, speculations as to future concepts and suggestions for broad and productive methods of approach in the study of psychopathology. The book is thoroughly interesting (in spite of rather frequent repetitions) but not always convincing. The review of recent developments, the papers on Individuality and Introversions and The Comparative Methods in Psychiatry are the most impressive essays.

A new point of view for the study of man is suggested. 1. Man is not separate and distinct from his fellows and environment but is a focus for forces that grow out of his environment and resolve back into it. 2. Man is an open energy system constantly receiving energy from the outside and giving energy back to it. 3. Man is to be thought of in terms of energy rather than of organs. For instance, death is a final equilibrium; tumors, like delusions, are energy manifestations uncontrolled by the organism; diseases are states of special energy stress or tension.

Existing tendencies indicate a growing dissatisfaction with kraepelinian classification and an increasing effort toward interpretative psychiatry. Recent developments are associated with the ideas of Kretschmer, Schilder, Jung, and Hoch, with Stransky taking a reactional position. The comparative method is being used to advantage in psychiatry as in neuro-anatomy; light is being thrown on the psychoses by the study of the methods of thinking of the child and of primitive man. While it is speculative, it is worth while, in considering the human organism as an energy system, to conceive that "any new problem of adjustment requires a redistribution of energy whereby stress may fall in new and different places and that organic disease may be related to this redistribution of stress."

The volume concludes with reviews of the adlerian concept, and book reviews of "Primitive Mentality," by Levy-Bruhl and "Elements of Physical Biology" by Lotka.

DIE NEUROSEN DES KINDESALTERS. By DR. W. CIMBAL. Price: Cloth, 15 marks; paper, 16.50. Pp. 490. Berlin: Urban & Schwarzenberg, 1927.

This is an excellent work, comprehensive in scope, clear in exposition and systematic in arrangement. The prevalence of a neurotic basis in the difficulties of learning and adjustment is pointed out and the necessity of a broader understanding of the neurotic child is stressed. This is to be accomplished by structure analysis, in which the basic components of the person as a whole are investigated by a coordinated physical, neurologic, endocrine, psychologic and psychiatric study.

The first portion of the book is devoted to a description of the various clinical manifestations of the neuropathies, neuroses and psychoses. Grouping, according to syndrome complex, is logically arranged and specific therapeutic measures are discussed at the end of each group. The second portion contains a detailed explanation of structure analysis and methods of examination. The chapters on the endocrines are particularly noteworthy. The third portion deals with therapeutic methods, determined by the investigation of the causative factors in the individual cases, which includes medicinal, physical, dietary and psychotherapeutic measures. While the prevalence of organic inferiority is emphasized, the importance of psychogenic factors and the value of psychoanalytic methods are appreciated and the organic and psychogenic concepts are brought together in a harmonious whole. This same broad point of view is reflected throughout in the discussion of the therapeutic measures, which is concise and systematically arranged.

As the title indicates, the Neuroses of Childhood forms the basis of this work yet the material lends itself almost equally well to a better appreciation of the personality make-up and behavior of the adjusted child and adult. The book is well worth the attention of every physician, regardless of the nature of his work, but will be of greatest value to those dealing with children and adolescents. It must be read to be appreciated and it can be given unreserved approval.

STUDIES IN PSYCHOLOGY AND PSYCHIATRY. June, 1926, volume 1.

This issue is devoted to the "Psychology of Reasoning" by Miriam Frances Dunn. It is divided into two parts: first, "Historical Outline," and second, "Experimental." The introduction of three and one-half pages sets forth in part the object of the contribution. The first part, "Historical Outline," has three chapters: "Philosophical and Non-Empirical Theories," "Experimental Work on Judgment and Inference," and "Theories of Logicians." The latter considers the points of view of Jevons, James Mill, John Stuart Mill, Schiller, Spencer, Bosanquet, Bradley, Wundt and Sigwart.

Part II on "Experimental Work in Reasoning" has four chapters devoted to the substance of the experiments, and a final chapter on the general summary of the results. Actual court cases were given to subjects to determine

their methods of reasoning, the judge's decisions in these cases being withheld. The conclusions are presented in tabular form in the third chapter, and in the fourth chapter the theories of the various authors, mentioned in part one, are taken up in a discussion of the tables of results. The concluding paragraph in the general summary is as follows: "The formal essential character of reasoning may be regarded as the insight into the necessary truth of the conclusions as dependent on the premises. This insight is an intellectual non-sensory experience." A bibliography of three and one-half pages is appended.

The first part of this work does not permit readily of abstracting, as it is in reality a review of the points of view of many authors. The second part on experimental work must be read in its entirety, as it contains a solid mass of information. It is worthy of a great deal of careful study, and the effort is unquestionably commendable.

HUMAN EFFICIENCY AND LEVELS OF INTELLIGENCE. By HENRY HERBERT GODDARD. Lectures delivered at Princeton University, April, 1919. Price, $1.50. Princeton, N. J.: Princeton University Press, 1920.

The first lecture on mental levels explains the difference between intelligence and knowledge, likening intelligence to printing presses of various stages of complexity and knowledge to the raw material fed to them. It speaks of the first method of determining intelligence of persons introduced by Binet about 1905 and explains the accuracy of various tests as determining mental level, quoting Army Alpha tests.

The second lecture is on efficiency, which consists in fitting people into work at the level of their intelligence, on their emotional control, temperament, and physical conditions. Ability to adapt one's self to one's environment is an index of mental level.

The next lecture is on the delinquent, or the person who neglects his duty. He impairs the efficiency of the group. He may be delinquent "because he does not know any better or because he cannot help it." There is the high percentage of low mental levels in criminals, misdemeanants, delinquents and other antisocial groups, with other factors such as insanity (dementia praecox) epilepsy and epileptic equivalents, mental conflict (Healy) and criminal environment. Change of surroundings and segregation are logical treatment because they attack the cause.

A discussion of democracy turns on whether we can hope to have a successful democracy where average intelligence is thirteen years (in the United States). How can the intelligent groups plan for the mass?

This book without bringing any new ideas presents its case with clearness and authority and is a good introduction to an important subject.

THE MENINGIOMAS ARISING FROM THE OLFACTORY GROOVE AND THEIR REMOVAL BY THE AID OF ELECTROSURGERY. MACEWEN MEMORIAL LECTURE, 1927. By HARVEY CUSHING, C.B., D.S.M. Price, 2 shillings, 6 pence. Pp. 53. Glasgow: Jackson Wylie & Co., 73 West George Street, 1927.

This small pamphlet of fifty-three pages is the subject of the MacEwen Memorial Lecture, 1927, delivered by Harvey Cushing. There is an attractive introduction in which the author traces the influence of the Glasgow School on surgery, particularly neurosurgery. He then gives an interesting description of meningiomas occurring in the olfactory groove, which, according to him, have a syndrome no less characteristic than primary suprasellar lesions. These tumors arise from the meninges of the anterior fossa of the skull, usually, though not always, in the midline. They are apt to be firm, even psammomatous in character.

The symptoms in these cases are almost characteristic. They consist of anosmia, usually unilateral but sometimes bilateral, primary atrophy, usually of one optic nerve but sometimes of both, mental symptoms due to involve-

ment of the inferior portion of the frontal lobe and sometimes erosion of the wings of the sphenoidal ridge, with at times enlargement of the sella shown by the roentgen ray. Of most interest, however, is the neurosurgical method described by Cushing. Heretofore, the removal of such tumors was a long and arduous task, the growth being removed piecemeal. In these operations, Cushing uses an electric cautery developed with the aid of Dr. Bovie. In three cases in which this method was used, the operations were carried through at a single session with preservation of the bone flap instead of multiple operations, as in the old methods. This new device has great possibilities, and it is hoped that the electrical surgical method for the removal of tumors will be further developed.

TRAVAUX ET MEMOIRES. Second Volume. By PROF. PIERRE MARIE. Price, 30 francs. Pp. 390. Paris: Masson et Cie, 1928.

This is the second volume of reprints of Pierre Marie's collected papers. The review of the first volume appeared in THE ARCHIVES (**18**:670 [Oct.] 1927). As in the first volume, the papers are republished as they originally appeared. Among the most noteworthy papers are the Charcot-Marie amyotrophies, cerebellar hereditary ataxia and lacunar sources of disintegration. Then follow a group of papers classified as follows: diseases of the encephalon, infections of the nervous system, diseases of the spinal cord, and miscellaneous affections.

L'ARCHITECTURE CELLULAIRE NORMALE DE L'ÉCORCE CÉRÉBRALE. By CONSTANTIN V. ECONOMO. French Edition by DR. LUDO VAN BOGAERT. Price, 80 francs. Pp. 184. Paris: Masson et Cie, 1927.

This book is the French translation from the German of Economo. A review of this work has already appeared.

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